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THE ACTIONS OF PROCAINE ON NEURO-MUSCULAR TRANSMISSION

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Submitted for publication April 27, 1939

Since experimental evidence definitely suggesting the function of acetylcholine in the transmission of excitation from nerve to voluntary muscle was advanced by Dale and his collaborators (1, 2), a renewed interest has been taken in the study of the pathogenesis of those human muscular diseases which are attributable to a defect in neuro-muscular conduction. Various drugs, which have been found experimentally to alter in some way the normal transmission of impulses at the neuro-muscular junctions, also have a striking action in myasthenia gravis and myotonia. Thus, eserine and potassium chloride are known to relieve the symptoms of myasthenia (3, 4) and to enhance their severity in myotonia (5, 6); while quinine has an opposite effect in these two diseases (5, 7).

It has been known for some time that procaine (Novocaine), like quinine, may cause an exaggeration of the weakness in the myasthenic state (8, 9), and there is sufficient evidence already available to suggest that some part, at least, of its action in this disease may be attributable to its curare-like action. Liljestrand and Magnus (10) were the first to investigate systematically the action of procaine upon the function of normal skeletal muscle. They found that decerebrate rigidity in cats was greatly reduced by small doses of this drug, although, at the same time, spontaneous muscular movements and the threshold for stimulation through the motor nerve were unaltered. Larger doses reduced the response of the muscle to stimulation of its motor nerve without altering the responses of the muscle to direct excitation with a faradic current. Analogous clinical observations were made by

[1] Medical Research Fellow of the American College of Physicians.

Walshe (11), who showed that the rigidity of paralysis agitans and spastic hemiplegia could be reduced by the intramuscular injection of procaine, without causing any impairment of voluntary power, or of the excitability of the muscle to direct stimulation.

Fulton (12) extended the observations of Liljestrand and Magnus. He found that the sciatic nerve of the frog could be immersed in a 5 per cent solution of procaine for thirty minutes with no alteration in its conductivity as judged by the responses of the muscles. If the solution was applied directly to the muscle, stimulation of the nerve no longer evoked a response; but the muscle still contracted readily to direct excitation. He drew attention to the similarity of the effects of procaine and of curare.

Bremer and Titica (13) similarly compared the action of procaine with the selective action of curare in feeble doses upon decerebrate rigidity, and the rigidity of a "local tetanus."

Riesser and Neuschloss (14) found that procaine abolished the response of frog muscle to the application of acetylcholine before that to electrical stimulation, and Frank, Nothmann, and Hirsch-Kauffmann (15) have shown that the reactions of denervated mammalian muscle to acetylcholine, nicotine and similar substances are suppressed by procaine.

Recent developments in technique have allowed the effects of acetylcholine and eserine on normal skeletal muscle to be studied in greater detail. In order to find an explanation of the action of procaine in myasthenia gravis, its effects upon neuromuscular transmission, and upon the responses evoked in normal mammalian muscle by acetylcholine and eserine have been studied, using the method of close arterial injection (2).

METHODS

These experiments were performed on cats decerebrated under preliminary ether anesthesia, and prepared for arterial injections into the tibialis anterior muscle (16). In the experiments on the denervated muscle, the sciatic nerve was cut aseptically under ether anesthesia and 10 to 15 days allowed for degeneration.[2]

Muscle contractions were recorded with a roughly isometric lever of the flat spring type, writing on a smoked drum by a light aluminium lever. The sciatic

[2] I am indebted to Dr. F. C. MacIntosh for the operations.

nerve, previously ligated high in the thigh, was left in position in the thigh muscles, and was stimulated through a shielded electrode. The stimuli were slightly supramaximal condenser discharges timed by means of a neon tube stimulator; tetanic and single stimuli were applied through separate electrodes. The cathodes of the two pairs were 2 cm. apart on the nerve, and each was distal to its anode. For direct stimulation of the muscle a silver pin was pushed through the tendon, and the drill piercing the condyles of the femur served as the other electrode; in this instance stimuli were break induction shocks timed by a Lewis rotating contact breaker.

The arrangements for electrical recording were essentially those reported in earlier papers from this laboratory (17). The leads from the muscle for the action potential following nerve stimulation were either two silver pins, one in the tendon connected to the input grid and the other, connected to earth, inserted into the belly of the muscle; or concentric needle electrodes, as described by Adrian and Bronk (18). The amplifier consisted of resistance-capacity coupled stages connected to four pentodes which actuated a Matthews oscillograph. With belly to tendon recording, two stages and large coupling condensers were used, while three stages and small coupling condensers were employed with the concentric needles.

In the experiments in which the superior cervical ganglion was perfused, the technique was that described by MacIntosh (19).

Procaine hydrochloride dissolved in saline (0.9 per cent), acidified with hydrochloric acid to pH 4, was used. Control injections of the solvent caused no alteration in the response of the muscles. The injection volume was always 0.25 cc. The eserine sulphate and potassium chloride were prepared in the same manner. Acetylcholine was always freshly prepared, in acid saline at pH 4, just before use.

RESULTS

Effects on responses to nerve stimulation and to direct excitation

Single twitches: Arterial injection of procaine, in doses between 0.2 and 1.0 mg., into the tibialis anterior muscle, reduces the tension of the twitches evoked by maximal motor nerve volleys delivered at 10 sec. intervals (Fig. 1). The depression becomes apparent immediately after the injection, and reaches its maximum within 30 to 60 sec. A small decrease is perceptible with 0.1 mg. and the twitches may be reduced to 40 to 60 per cent of their previous tension by the injection of 1.0 mg. of the drug. The change is not a permanent one, and the twitches gradually regain the original tension over a period of a few minutes, the actual duration of the depression depending on the amount of drug administered. Subsequent injections cause a further and permanent depression of the response to single nerve volleys.

The diminution in the twitch tension with doses in this range is entirely due to depression of neuromuscular conduction. This is proved by the fact that, in these doses, the drug usually causes no appreciable change in the response of the fully curarized or denervated muscle to a single shock. With larger amounts (1.0 to 2.0 mg.) a slight depression of such directly excited twitches appears, but the effect is very small, in comparison with that produced by a similar dose when the muscle is excited indirectly through its motor nerve. With small doses (0.1 to 0.5 mg.) a slight potentiation of the directly

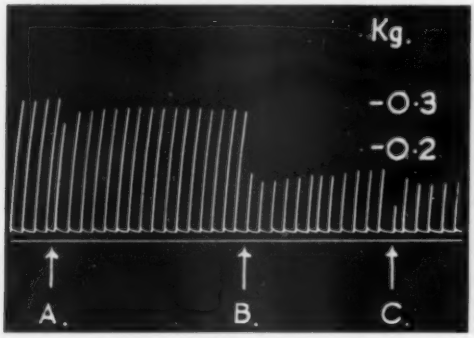

FIG. 1

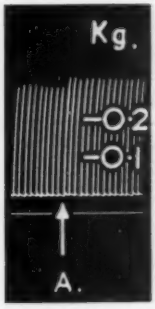

FIG. 2

FIG. 1. Cat, decerebrate, 2.6 kg. Maximal motor nerve stimuli of tibialis anterior muscle every 10 sec. Intra-arterial injections: at *A* and *C*, acetylcholine 10 μg; at *B*, procaine 1 mg.

FIG. 2. Cat, decerebrate, 2.1 kg. Maximal stimuli directly to muscle every 10 sec. Curarine, 1.8 mg., intravenously. No response to stimulation of motor nerve. At *A*, procaine 0.5 mg.

excited twitches has been observed (Fig. 2). A similar, very small potentiation, even of twitches excited by nerve volleys, has in rare instances been observed to follow a first, small injection of procaine (Fig. 3B).

Tetanus: The tetanic response of a muscle to a series of nerve volleys is greatly depressed by the administration of procaine (Fig. 3). After a single injection of 0.5 mg. a series of maximal shocks applied to the nerve at 50 per second causes the development of little more tension than that of a single twitch, and the muscle relaxes rapidly during the

stimulation (Fig. 3, E). This effect on the response to repetitive stimulation of the nerve is longer in duration than that on the single twitch, and a muscle which has received an injection of the drug does not regain its ability to respond normally to a motor nerve tetanus, during the ordinary duration of an experiment.

This effect on the response to indirect tetanization is again due to an action of procaine upon neuromuscular transmission. Denervated muscle responds perfectly well to direct tetanization after treatment

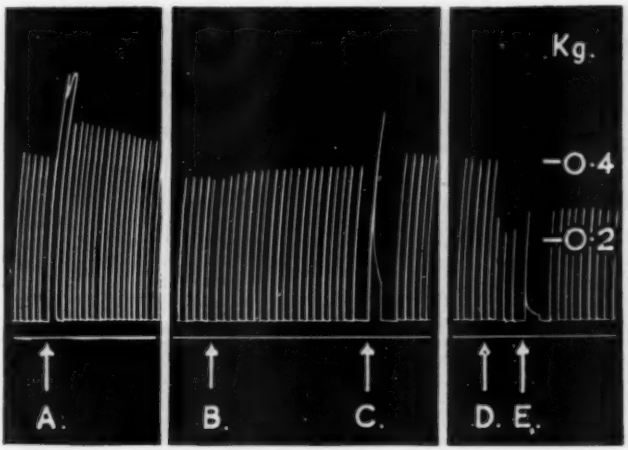

FIG. 3. Cat, decerebrate, 3.0 kg. Responses of tibialis anterior muscle to maximal motor nerve stimuli every 10 sec. At *A*, *C* and *E* responses to tetanization of the motor nerve for 10 sec. at 50 per sec. Intra-arterial injection of procaine; at *B*, 200 μg. and at *D*, 500 μg.

with procaine (Fig. 4). In this case, the response evoked by repetitive stimulation is not appreciably altered by a single dose of procaine. After several injections the tension maximum is somewhat reduced, but there is no such alteration in the twitch-tetanus ratio as with stimulation through the nerve. The potentiation of single maximal twitches of a muscle, following a brief period of tetanus, has been described by Brown and Euler (20), and shown to occur also in denervated muscle. This post-tetanic potentiation of denervated muscle is not abolished by the administration of procaine (Fig. 4).

In this figure the diminishing post-tetanic potentiation, after the muscle has received several tetani, is no more than is normally seen in denervated muscle. Although the size of the twitches gradually diminishes, the twitch-tetanus ratio remains fairly constant; and even in figure 4C there is a small but definite potentiation after the tetanus.

Sufficient evidence has been advanced to show that procaine has effects on mammalian muscle very like those of curarine, and in another respect the reactions of a muscle treated with procaine very

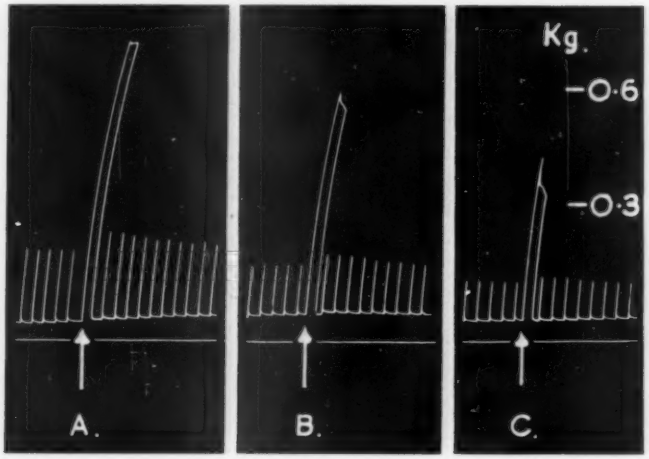

FIG. 4. Cat, decerebrate, 2.4 kg. (denervated 8 days). Maximal direct stimuli of tibialis anterior muscle every 10 sec. At *A*, *B*, and *C*, direct stimulation at a frequency of approximately 50 per sec. for 10 sec. One minute preceding each tetanus 0.5 mg. of procaine was injected intra-arterially.

closely resemble those of a weakly curarized muscle. Boyd (21) has shown that the interpolation of a brief tetanic stimulation of a motor nerve can produce relief of a partial curare paralysis. Brown and Euler (20) have demonstrated that this is due to a long lasting restoration of end-plate excitability, whereby single volleys falling after a tetanus are able to excite additional muscle fibres.

A similar phenomenon is seen after depression by procaine. The experiment illustrated in figure 5 shows more than one resemblance

between the action of procaine and curarine. The response of the muscle to maximal nerve volleys, applied at 10 sec. intervals as usual, had first been reduced by an incompletely paralytic intravenous dose of 1.5 mg. of curarine. When this effect had reached a steady level, 0.25 mg. of procaine, injected arterially into the muscle at B, showed an additive curarizing action, annulling the nerve twitches completely, but leaving the response to a series of directly applied shocks, at C, unaffected. The nerve volleys at 10 sec. intervals being then re-

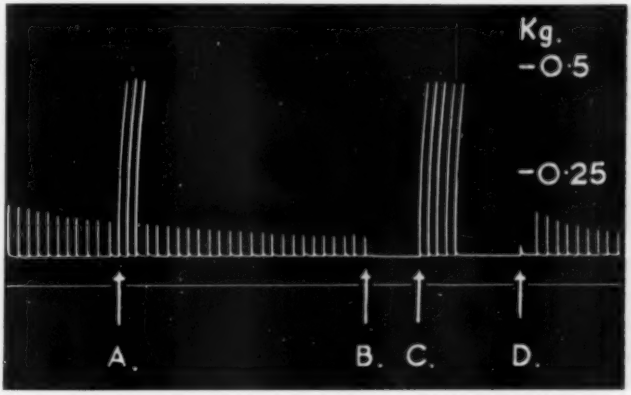

FIG. 5. Cat, decerebrate, 2.1 kg. Maximal motor nerve stimuli of tibialis anterior muscle every 10 sec. Curarine 1.5 mg. intravenously. At *A*, three maximal stimuli directly to the muscle. At *B*, procaine, 250 μg. At *C*, five direct stimuli. At *D*, tetanization of the motor nerve at 50 per sec. for 6 sec.

sumed, still without effect, a 6 sec. burst of shocks at 50 per sec. was applied to the nerve at D. The tetanic response itself was very weak and not maintained, as was to be expected; but when, 10 sec. after the tetanization had ended, the single nerve volleys were resumed, the twitches had not only reappeared, but had even recovered a tension greater than that to which curarine alone had reduced them. In other words, the depressant effect of procaine on the neuromuscular transmission further resembled that due to curarine in being relieved by the after-effect of a brief tetanization through the nerve, even though the immediate response to the latter was minimal.

Effects on the responses to acetylcholine and potassium chloride

It has been shown by Brown and his collaborators (2) that the tension response of the normal cat's gastrocnemius muscle to a close arterial injection of 5 to 10 μg. of acetylcholine, is almost always greater than that evoked by a maximal motor nerve volley. They also demonstrated that a dose of curarine which had only a small effect on the twitch response to nerve stimulation, would greatly reduce an approximately equal contraction caused by the injection of acetylcholine.

The contraction resulting from the injection of acetylcholine is also greatly diminished by the administration of procaine (Fig. 1). In this regard, the action of procaine parallels that of curarine, except that the depression of the response to acetylcholine is not so greatly in excess of the depression of the twitch response. In the experiment from which figure 1 was taken, when the nerve twitches had returned to their normal level, the tension response to injected acetylcholine had also regained its original value. By contrast, the reponse to an injection of potassium chloride, which, in doses about 1000 times as great, produces an effect superficially very similar to that of acetylcholine (22), is unaffected by procaine, as by curarine, in doses which in both cases greatly depress the normally equivalent response to acetylcholine.

Effect on the response of denervated muscle

The response of the denervated mammalian muscle to an arterial injection of acetylcholine is double in character; a quick contraction, of the nature of a burst of asynchronous tetanus, being followed by a slower contracture (2). Both phases of this response are greatly reduced by a single arterial injection of 0.5 mg. of procaine. After a second, similar dose, the contracture is usually completely abolished, and the quick response reduced to less than one-half of its original tension.

Effect on eserine potentiation

Brown and his collaborators (2) described the potentiating effect of eserine on the maximal motor nerve twitch, and found that it was due to a repetitive response causing a short, declining tetanus. They

attributed this effect to a diminution in esterase activity, which allowed the acetylcholine liberated by a single volley to disappear slowly from the region of the motor end-plates.

When a small dose of procaine is injected into a muscle during eserine potentiation, the twitches are immediately reduced (Fig. 6, B). Recovery, however, rapidly follows, and after two to three minutes the full tension of the potentiated twitches is regained. A second dose of procaine (Fig. 6, C) again reduces them to the normal tension, at which they remain. On the other hand, if eserine is administered to a muscle which has previously been injected with procaine, the potentiating effect of the drug is replaced by a slight depression of the twitch tension (Fig. 6, D).

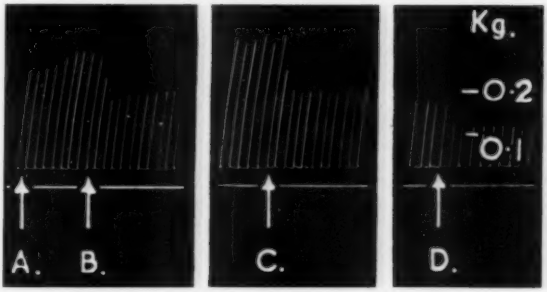

FIG. 6. Cat, decerebrate, 2.9 kg. Maximal motor nerve stimuli every 10 sec. Intra-arterial injection: at *A* and *D*, eserine 25 μg.; at *B* and *C*, procaine 250 μg.

When the action potential of the muscle under eserine in response to a single maximal nerve volley is recorded, the main negative spike is followed by a series of small waves lasting over a period of about 60 msec. (17). When procaine is administered intraarterially, this repetitive discharge is abolished, and, in addition, the negative wave recorded with belly to tendon leads is diminished in size, indicating that fewer muscle fibers are contracting. The significance of this observation will be considered in the discussion.

Effect on responses of the superior cervical ganglion

Brown and Feldberg (23) showed that curarine, perfused in suitable concentration through the superior cervical ganglion, abolished the

response of the ganglion cells to preganglionic impulses and to injection of acetylcholine into the perfusion fluid, but not to the otherwise similar stimulating effect of potassium chloride. By analogy with the observations of Feldberg and Vartiainen (24) on the similar paralytic action of nicotine on the ganglion, and with those of Dale and others (1) on the action of curarine on voluntary muscle, it may be supposed that curarine does not interfere with the liberation of acetylcholine by preganglionic impulses arriving at the synaptic endings.

Procaine added to the perfusion fluid prevents, like curarine, the transmission of impulses through the ganglion, as shown by failure of the nictitating membrane to respond to preganglionic stimulation (Fig. 7). When the ganglion is perfused with Locke's solution containing eserine, and the venous effluent is collected, it is found, however, that procaine also prevents the output of acetylcholine during preganglionic stimulation. For example, in one such experiment the quantity of acetylcholine appearing in the venous fluid, during a control period of 5 minutes' preganglionic stimulation, was about 0.1 μg. A second equal period of stimulation was given during the slow addition of 0.5 mg. of procaine to the perfusion fluid—a quantity sufficient to abolish the transmission of impulses, as shown by the failure of the nictitating membrane to contract; and during this period no acetylcholine could be detected in the venous fluid by the sensitive leech test. Perfusion was continued without further procaine, and without interruption of the preganglionic stimulation. One minute after the addition of procaine to the perfusion had been completed, transmission through the ganglion again became effective, as shown by the sudden renewal of the response of the nictitating membrane, and a further sample of the venous fluid showed that the output of acetylcholine had then been likewise renewed.

This depression of the output of acetylcholine by preganglionic impulses, which may be taken to indicate an action of procaine on the endings of the preganglionic fibres, must obviously play a part in its action in interrupting synaptic transmission in the ganglion. It does not, however, represent its only effect in this direction. Procaine readily abolishes the response of the ganglion cells to acetylcholine. In one experiment the injection of 2 μg. of acetylcholine,

into the arterial cannula carrying Locke's solution with eserine to the ganglion, caused an almost maximal retraction of the nictitating membrane. After 0.5 mg. of procaine had been injected, doses of 2, 4 and 6 μg. of acetylcholine produced no response. In this case again,

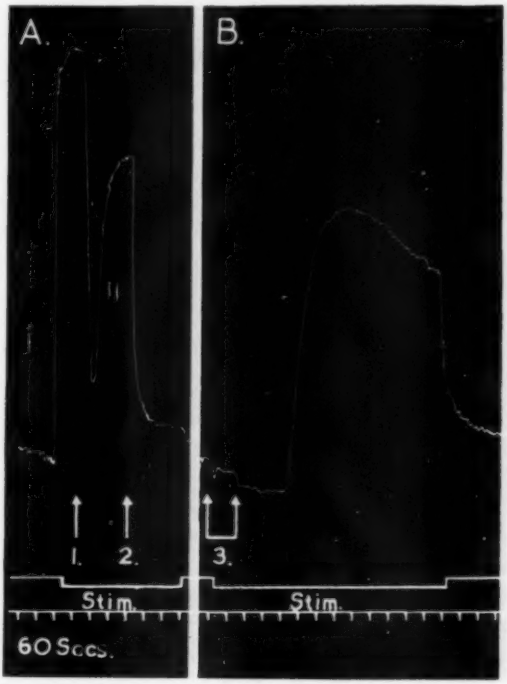

FIG. 7. Cat, decerebrate, 3.4 kg. Response of the nictitating membrane to maximal stimulation of the preganglionic nerve at a rate of 10 per sec. Injections of procaine into the perfusion fluid at 1, 50 μg. and at 2, 100 μg. During period 3, 0.5 mg. of procaine was slowly injected.

however, the depression of the response of the ganglion cells was less specifically limited than by curarine; the stimulating effect of 2 mg. of potassium chloride, initially comparable to that of 2 μg. of acetylcholine, was also greatly reduced by the treatment of the ganglion with procaine, though not abolished.

Altogether, it would appear that the action of procaine on the ganglion, while it renders the nerve cells insensitive to the stimulus of acetylcholine as curarine does, has a more general depressant effect on their activity, as shown by the reduced response to potassium chloride. The action of procaine also appears to extend to the preganglionic nerve endings, interfering with the liberation of acetylcholine from them by impulses.

DISCUSSION

The foregoing sections have made it clear that, in the main feature of its action on the mammalian muscle-nerve preparation, procaine resembles curarine, blocking neuro-muscular transmission and leaving unimpaired the response of the muscle to direct stimulation. Like curarine, procaine causes a specific depression of the response of the motor end-plate to acetylcholine; but the question arises whether, unlike curarine, it also acts on the terminal branches of the motor nerve fibres and thus interferes with the liberation of acetylcholine, as well as with its stimulant action. The most familiar action of procaine, in which it paralyses the endings of sensory nerve fibres, makes such an action on motor nerve terminals not unlikely; and the directly observed suppression of the output of acetylcholine from the synaptic endings of preganglionic fibres provides a suggestive analogy. It has further been noted that, while curarine only weakens the effects of maximal nerve volleys, in a dose which already annuls the roughly equivalent tension response to an artificial injection of acetylcholine, this disparity, though present, is much less obvious in the action of procaine; and this would be expected if, in its action on nerve-twitches, a strictly curare-like action of procaine, on motor end-plates, were reinforced by a depressant action on motor nerve endings. We have seen that when procaine is injected into a muscle, the responses of which to maximal single nerve volleys have been converted into short bursts of tetanus by eserine, the repetitive character of such responses is abolished, and that, in addition, the height of the now single wave of electrical potential is reduced below the normal, showing that not all the fibres of the muscle now respond to each maximal volley. This evidence would clearly be compatible with the suggestion that procaine exercises its depressant action on motor nerve endings,

as well as on motor end-plates of muscle fibres; on the other hand, a simple raising of the threshold of motor end-plates would be expected to produce the whole effect, removing the repetitive character of the response and reducing the number of muscle fibres concerned in it, as curare itself does in appropriate dosage. In default of direct evidence, therefore, we are only entitled to conclude, from the analogy of the known action of procaine on nerve fibres of other kinds and from its action on preganglionic nerve terminals, that its action probably extends to motor nerve endings, and is thus less specific and restricted than that of curare.

One other item of evidence, however, deserves mention. The response to single nerve volleys of a muscle under eserine is depressed by a period of tetanus, and this depression has been attributed to accumulation of acetylcholine in the muscle during the tetanus (25). This after-depression following a tetanus persists in the muscle under eserine when procaine has been given in addition; and this fact suggests that the depressant effect of procaine, in the doses we have given, on motor nerve endings in muscle, if it exists at all, is weaker than the depressant action on preganglionic nerve endings, observed under the conditions of application of procaine to the ganglion in these experiments.

Another substance, which, like procaine, is characterised by its deleterious effects on the myasthenic subject, is quinine, and I have earlier shown that its main effects in myasthenia can also be attributed to its curare-like action (26, 27). On normal muscle, however, the curare-like action of quinine was entirely masked by its potentiating effect on the tension developed by the single muscle twitch. Procaine also, but to a very much less degree, shows this potentiating effect on the single twitch, and this again, as in the case of quinine, is a phenomenon independent of the neuro-muscular transmitting apparatus, since it occurs in denervated and fully curarized muscles, and is then the only effect seen with moderate dosage.

These two substances, quinine and procaine, both possess in varying degrees curare-like actions and potentiating actions on the single twitch. Their curare-like actions are best demonstrated when they are administered to a preparation in which neuro-muscular transmission has been already depressed by curarine itself. It is perhaps

significant, therefore, that these two substances should have such strikingly depressant actions in myasthenia gravis and so little action on the normal subject. The old conception of myasthenia as a condition resembling curare poisoning (28), in which the primary lesion is a change in the excitability of the motor end-plates of the muscle, receives some support from these experiments.

SUMMARY

(1) The effects of procaine upon the responses of the tibialis anterior muscle of the cat to nerve stimulation, and to the injection of various drugs has been studied.

(2) This drug depresses the response of the muscle to nerve stimulation without affecting that to direct excitation; it reduces the response to tetanic stimulation of the nerve to little more than a single twitch; it reduces the contraction evoked by the injection of acetylcholine without greatly affecting that resulting from potassium chloride; it abolishes the eserine potentiation. These actions are similar to those of curarine.

(3) The depressed responses to nerve stimulation after an injection of procaine can be restored to normal by the interpolation of a brief tetanization of the motor nerve even though little or no mechanical response results.

(4) Procaine abolishes the responses of the superior cervical ganglion of the cat to stimulation of the preganglionic nerve fibres, and also suppresses the normal output of acetylcholine during such stimulation.

(5) The response of the superior cervical ganglion to the injection of acetylcholine is absent after the administration of procaine, and that to potassium chloride is greatly reduced.

(6) These effects of procaine are discussed in relation to the action of this drug in myasthenia gravis.

I wish to express my appreciation to Sir Henry Dale and Dr. G. L. Brown for their stimulating interest during these experiments.

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SQUAMOUS METAPLASIA, SIMULATING CARCINOMA, ASSOCIATED WITH PROSTATIC INFARCTION

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Squamous cell metaplasia and infarcts of the prostate have been described independently by several authors but the frequent coexistence of these two pathologic processes has been overlooked by previous investigators. In the recent routine study of a prostate removed by operation islands of squamous epithelium were noted along the margins of 3 infarcts. The provisional diagnosis was early squamous cell carcinoma. Further study of the remainder of the prostate showed only typical glandular hyperplasia. Eight additional prostatic infarcts, occurring in 7 different cases, were studied and in each instance similar histologic changes were seen, limited to the periphery of the infarcted areas. The uniformity of these findings indicates that benign metaplasia frequently is associated with prostatic infarction and may be misinterpreted as carcinoma.

Much has been written concerning infarction in general, but prostatic infarcts have received very little attention. Abeshouse (1933) presented the first study of infarcts of the prostate and reported 3 cases. He suggested that the etiological factors were (a) distortion of the glandular and vascular elements by benign or malignant adenomata, (b) infection, (c) instrumentation and pressure from indwelling urethral catheters, (d) circulatory disturbances in the perineal and prostatic region secondary to a general vascular disease, (e) localized areas of necrosis or suppuration within benign hypertrophy. Abeshouse also pointed out the difficulty of making a correct differential diagnosis between the tissues encountered in these cases of infarction and early carcinoma. The latter had been the pathologists' report on 2 of his cases, but he attributed the histologic findings to areas of compressed and distorted acini and ducts. No mention was made

in any of these cases of the metaplastic changes which will be considered in detail later.

Kasman and Gold (1933) reported 2 cases of metaplasia in the prostate, in one of which a central area of infarction was described. As far as we have been able to determine, this isolated case is the only previous record of metaplasia associated with prostatic infarction.

Hubly and Thompson (1938) reported 10 cases of infarction of the prostate but confined most of their discussion to its clinical significance. They suggested that the temporary inability of some patients to urinate after removal of the urethral catheter following transurethral resection was due to increase in prostatic volume caused by the transudation of fluid into regions of infarction. These writers favored the following etiological factors: (a) trauma, e.g., instrumentation and prostatic massage; (b) disturbances in the intraglandular vascular supply by adenomatous hyperplasia; (c) infection, particularly prostatitis; (d) stasis in the periprostatic plexus of veins, due to bed rest or general circulatory failure; (e) arteriosclerosis, (f) embolism. Unfortunately, the histology was described in only 1 of these 10 cases. In that instance, "the swelling in the region of infarction had pressed the acini at the periphery into strands in such a manner as to suggest carcinoma." Metaplasia was not mentioned in any of the cases.

No doubt infarction of the prostate is much more common than these few reports imply. The gland is a very vascular organ and should be a ready site for infarcts. Some probably have been identified only as areas of necrosis. Serial sections of operative and postmortem specimens undoubtedly would reveal more infarcts.

The following 8 cases illustrate the surprising incidence of metaplasia in instances of prostatic infarction and the ease with which erroneous diagnoses of carcinoma may be made. The first 4 cases were discovered during the routine study of specimens removed by operation.

Case 1. B.U.I. No. 27874. *Clinical Course:* A white man, aged 72, was admitted to the Brady Urological Institute, December 10, 1938, complaining of hematuria. Two weeks previously he had had an attack of acute urinary retention and had been catheterizing himself 2 to 3 times daily since that time. On the day preceding admission he began to bleed from the urethra. Physical examination was essentially negative except for a palpable bladder and a greatly

enlarged prostate which in some areas suggested carcinoma. Catheterization revealed 2,000 cc. of bloody urine. An attempt was made to control the bleeding with an hemastatic catheter but it drained poorly because of numerous intravesical blood clots. An effort to evacuate these clots by cystoscopy was unsuccessful. Two days after admission suprapubic cystostomy was performed under local anesthesia and the bleeding was stopped by gauze packs in the vesical orifice. The patient was given 2 transfusions (600 cc. and 500 cc.) of citrated blood the same day and made an uneventful recovery. The packs were removed on the third postoperative day with no subsequent bleeding. Later rectal examinations revealed disappearance of the indurated areas which suggested malignancy on admission (these probably were the congested infarcts which later had undergone softening). X-ray showed no evidence of metastases. On December 28, 1938, perineal prostatectomy was performed under spinal anesthesia and 110 grams of tissue were removed. The postoperative convalescence was uneventful except for the occurrence of a stricture in the membranous urethra which responded promptly to urethral dilatations. The patient was discharged February 14, 1939, with all incisions healed, and with no incontinence, frequency or difficulty in urination. On May 24, 1939 (5 months after operation) he continued to have no evidence of metastases.

Pathology (No. 10896): The specimen consisted of a right lateral lobe measuring 4 x 5 x 5.5 cm., a left lateral lobe measuring 4 x 2 x 3.5 cm., and a well defined median lobe 1.5 cm. in diameter. On the external surface and on cross-section, numerous small spheroids were seen in both lateral lobes. In the center of the right lobe was a sharply outlined, firm, homogeneous, pale yellow area, 2.5 x 1 cm., surrounded by a narrow zone of dark reddish brown tissue. A similar area 2 x 0.8 cm. was noted in the center of the left lobe. The median lobe had been replaced almost entirely by a similar pale yellow mass with a dark red periphery. Microscopically all 3 of these sharply demarcated areas proved to be typical infarcts. The central portion of each was composed of necrotic tissue with innumerable red blood cells. The usual zone of congestion was noted along the well defined margins and just beyond this all 3 of the infarcts were surrounded by an irregular zone of compressed glandular acini and islands of squamous epithelium. The latter were arranged in solid masses of varying sizes and shapes with some variation in staining characteristics. No epithelial pearls were seen, but the impression was that the squamous cells represented early carcinoma.

Original Diagnosis: Early squamous cell carcinoma of the prostate. Multiple prostatic infarcts. Benign prostatic hypertrophy. Chronic prostatitis.

Re-examination: The remainder of the prostatic tissue shows only typical benign glandular hyperplasia with numerous foci of leucocytic infiltration. All of the squamous epithelium is confined to the periphery of the infarcts and while a few areas suggest invasion of the surrounding stroma (Figs. 1 and 2), detailed study shows that most of the islands of squamous cells are sharply demarcated.

Final Interpretation: Benign prostatic hypertrophy. Chronic prostatitis. Multiple prostatic infarcts. Squamous cell metaplasia.

Case 2. B.U.I. No. 21308. (*Note:* This was the third infarct of the prostate included in the report by Abeshouse). *Clinical Course:* A white man, aged 69, entered the Brady Urological Institute, January 29, 1932, in acute urinary retention. Examination was essentially negative except for suprapubic tenderness and marked enlargement of the prostate. No areas suggestive of carcinoma were palpated. Catheterization revealed 725 cc. of clear urine. Cystoscopy showed marked intravesical and intraurethral hypertrophy of the lateral lobes of the prostate and a definite median lobe. Two days after admission the patient developed bilateral broncho-pneumonia. He was kept on indwelling urethral catheter drainage until perineal prostatectomy was carried out on February 24, 1932, under spinal anesthesia. Forty grams of prostatic tissue were removed. The patient made an uneventful recovery and left the hospital March 11, 1932, with his incision entirely healed, excellent urinary control, and no frequency or difficulty in urination. He returned for examination on March 26, 1939 (7 years after operation). There had been no recurrence of any of the urinary symptoms; and X-ray pictures at that time showed no evidence of carcinoma.

Pathology (No. 8242): The specimen consisted of 4 pieces of prostatic tissue, the largest of which measured 5 x 3.5 x 3 cm., and the smallest 1 x 1 x 1 cm. Macroscopically it presented only dense fibrous tissue in which a few small spheroids were identified. The tissue appeared somewhat homogeneous in many areas, especially the median lobe. Sections from the 2 lateral lobes showed a dense stroma in which there was marked hyperplasia of the glandular epithelium without invasion of the surrounding tissue, or leucocytic infiltration. The section from the median lobe revealed a typical infarct, 1 cm. in diameter, and a few distorted glandular structures. In the original report no mention was made of any squamous epithelium.

Original Diagnosis: Benign prostatic hypertrophy. Organized prostatic infarct.

Re-examination: Along the margin of the infarct there are several small islands of squamous epithelium similar to that described in Case 1 (Fig. 3). Although compressed acini may be identified near the area of infarction, this squamous epithelium can be accounted for only on the basis of cellular metaplasia. Again the changes are limited to the region immediately surrounding the infarct.

Final Interpretation: Benign prostatic hypertrophy. Infarct of the median lobe. Squamous cell metaplasia.

Case 3. B.U.I. 23210. *Clinical Course:* A white man, aged 73, entered the Brady Urological Institute, April 18, 1934, complaining of hematuria and difficulty in urination. Physical examination was negative except for moderate enlargement of the prostate, which was elastic throughout, and a large hydrocele. Cystoscopy revealed 10 cc. residual urine, slight intraurethral hypertrophy of the prostate, and 2 papillary tumors on the posterior wall of the bladder. The bladder tumors were interpreted as malignant papillomata and were treated intensively with fulguration and intravesical radium. The patient developed marked urinary

difficulty and the residual urine increased to 100 cc. A punch operation was carried out under local anesthesia on May 17, 1934, but the patient was unable to urinate after removal of the urethral catheter. Suprapubic prostatectomy was performed June 6, 1934, under spinal anesthesia, and 39 grams of tissue were removed. No evidence of tumor was seen on exploration of the bladder. The patient's postoperative convalescence was uneventful except for delayed wound healing. He left the hospital asymptomatic on July 31, 1934. The patient died at his home on August 1, 1935. Autopsy was performed by the attending physician and no evidence of tumor or metastases was found. The immediate cause of death was a large pulmonary abscess.

Pathology (No. 9077): The operative specimen consisted of both lateral lobes, each measuring 4 x 3 x 2.5 cm., and a median lobe 1.5 cm. in diameter. Numerous small spheroids were seen on the cut surface of each lobe. In the left lateral lobe a homogeneous, discolored area, 0.7 cm. in diameter, was noted. Sections through this sharply demarcated area showed localized necrosis surrounded by small, solid accumulations of squamous cells which were thought to represent early carcinoma. The remainder of the prostate showed diffuse benign glandular hyperplasia and a few foci of leucocytic infiltration.

Original Diagnosis: Squamous cell carcinoma of the prostate. Benign prostatic hypertrophy. Chronic prostatitis.

Re-examination: The necrotic tissue is found to be a typical, small, prostatic infarct similar to those noted in the other cases. The islands of squamous epithelium are confined to the periphery of the infarct and present the same histologic characteristics as those described in the preceding cases. No definite invasion of the surrounding stroma is seen. The remainder of the tissue shows only glandular hyperplasia and chronic infection.

Final Interpretation: Benign prostatic hypertrophy. Chronic prostatitis. Infarct of the left lateral lobe. Squamous cell metaplasia.

Case 4. B.U.I. 23337. *Clinical Course:* A colored man, aged 73, entered the urological service September 27, 1934, complaining of difficulty in urination. Examination revealed generalized arteriosclerosis, tenderness in the suprapubic region, and a markedly enlarged prostate of first degree induration. Catheterization disclosed 250 cc. residual urine. The patient was unable to tolerate the indwelling urethral catheter and perineal urethrostomy was carried out October 10, 1934, under local anesthesia. The blood urea gradually dropped from 60 to 36 mg. per 100 cc. A perineal prostatectomy was performed on November 2, 1934, under spinal anesthesia, and 129 grams of prostatic tissue were removed. The patient's convalescence was uneventful and he left the hospital, December 3, 1934, in excellent condition. The patient returned for examination on May 19, 1939 (4½ years after operation) and had no clinical or X-ray evidence of carcinoma.

Pathology (No. 9213): The specimen consisted of a right lateral lobe, measuring 4 x 5.5 x 3 cm., a left lateral lobe, measuring 5 x 4 x 5 cm., and a median lobe, 2 cm. in diameter. On cross section all of the lobes showed abundant milky fluid,

numerous small spheroids, and a small abscess was noted in the left lateral lobe. Microscopic sections showed diffuse glandular hyperplasia throughout each lobe and many small accumulations of leucocytes. In the right lateral lobe a small area of necrosis was noted, around which there were irregular masses of squamous epithelium. These were interpreted as "undoubtedly small areas of beginning carcinoma."

Original Diagnosis: Benign prostatic hypertrophy. Chronic prostatitis. Early squamous cell carcinoma of the prostate.

Re-examination: The small necrotic area in the right lateral lobe is found to be a typical, sharply demarcated, prostatic infarct, 0.6 cm. in diameter. Along the periphery of this infarct there are several irregular, solid accumulations of squamous cells without pearl formation or definite invasion of the surrounding stroma. These cells are similar in every way to those described in the other cases of metaplasia. All of the squamous epithelium is confined to the margin of the infarcted area and the remainder of the prostate shows only benign glandular hyperplasia and chronic infection.

Final Interpretation: Benign prostatic hypertrophy. Chronic prostatitis. Infarct of the right lateral lobe. Squamous cell metaplasia.

Through the courtesy of Dr. B. S. Abeshouse, the additional 2 cases of prostatic infarction which he reported were studied and are summarized below.

Case 5. Clinical Course: A white man, aged 72, entered the Sinai Hospital, September 22, 1930, complaining of urinary difficulty. For 1 year he had received prostatic massage for chronic prostatitis, and following massage 10 days prior to admission he suddenly developed urinary frequency, urgency, hesitancy and burning which resulted in acute retention the following day. Interval catheterization was employed for 4 days, followed by an indwelling urethral catheter for the 5 days immediately preceding hospitalization. Examination revealed a slightly enlarged prostate with no suggestion of abscess or malignancy. On October 29, 1930, perineal prostatectomy was performed under caudal anesthesia. The patient had an uneventful convalescence and left the hospital December 14, 1930, with an excellent result. Later examinations revealed a negative prostate; and X-ray pictures on September 8, 1938 (8 years after operation) showed no evidence of malignancy.

Pathology (No. 6030): The specimen consisted of 2 pieces of prostatic tissue measuring 4.5 x 4 x 3 cm., and 1 x 1.5 x 0.5 cm. On cross section the lateral and median lobes showed many small spheroids and in the center of the right lateral lobe there was a well defined abscess, 0.5 cm. in diameter. In the center of the left lateral lobe there was a hemorrhagic area 1 cm. in diameter. The original pathological report described an area of necrosis in the left lateral lobe surrounded by new duct formation and numerous cord-like, solid masses of cells which were

interpreted as early carcinoma. The remainder of the prostate showed only adenomatous hyperplasia and several small abscesses.

Original Diagnosis: Early carcinoma of the prostate. Chronic prostatitis. Prostatic abscesses. Infarct of the prostate.

Re-examination: Abeshouse studied these sections at the time of his report (1933) and interpreted this suspicious area as merely a collection of compressed glands and ducts. Re-examination of the tissue, however, reveals very definite alteration in the morphology of the epithelium along the periphery of the infarct. There are many irregular, solid masses of transitional cells and squamous cells similar to those noted in the preceding cases. Although many compressed and distorted acini are seen, these cellular changes can be attributed only to metaplasia.

Final Interpretation: Benign prostatic hypertrophy. Chronic prostatitis. Prostatic abscesses. Infarct of the left lateral lobe. Squamous cell metaplasia.

Case 6. Clinical Course: A white man, aged 70, was admitted to the Sinai Hospital, September 9, 1930, complaining of urinary difficulty. For 10 years he had been under treatment for angina pectoris. Three days before admission he developed acute urinary retention and the bladder was decompressed slowly. The patient failed to tolerate the indwelling catheter and 2 days after admission suprapubic cystostomy was performed under spinal anesthesia. Several hundred small calculi, varying in size from pin-head to a pea, were removed from the bladder. The postoperative convalescence was uneventful except for delayed wound healing. On October 17, 1930, a second stage suprapubic prostatectomy was done under spinal anesthesia. The patient died 10 hours after operation of acute myocardial failure. Permission for an autopsy was not obtained.

Pathology (No. 6007): The combined lateral and median lobes measured 5.5 x 5.5 x 5 cm. On cross section each lobe showed many small spheroids. In the center of the right lateral lobe was an abscess 4 mm. in diameter. Near the center of the left lateral lobe was a sharply circumscribed, grey area, 1.5 cm. in diameter, surrounded by a zone of fibrotic tissue with some hemorrhagic extravasation. In the original pathological report, sections from the left lateral lobe were said to show "cells arranged in cord-like forms which suggested carcinoma." The remainder of the prostate showed acute and chronic prostatitis and diffuse adenomatous hyperplasia.

Original Diagnosis: Early carcinoma of the prostate. Acute and chronic prostatitis.

Re-examination: Abeshouse studied these sections and found a typical infarct in the left lobe. He interpreted these questionable cells as "an area of coagulative necrosis wherein the cellular changes in the prostatic epithelium resulted in a disorderly arrangement and an irregularity in the size of the cells." Re-examination of these slides, however, shows unquestionable alteration in the morphology of the cells surrounding the infarct. The metaplasia has been to transitional and squamous epithelium similar to that noted in the other cases. (Fig. 4).

Final Interpretation: Benign prostatic hypertrophy. Acute and chronic prostatitis. Infarct of the left lateral lobe. Squamous cell metaplasia.

The following infarcts of the prostate were found in 2 autopsies during the period of this study. They showed metaplastic changes similar to those described above.

Case 7. B.U.I. No. 18622. *Clinical Course:* A white man, aged 75, entered the Brady Urological Institute, September 6, 1938, because of urinary retention. Since 1926 he had been hospitalized 3 times with hypertension, arteriosclerosis, cardiac hypertrophy and decompensation, and dilatation of the aorta. Two days before admission he developed acute urinary retention and was catheterized twice daily until he entered the hospital. On admission he was disoriented, and examination revealed emphysema, cardiac enlargement, fecal incontinence, cachexia, generalized arteriosclerosis, hypertension (210/120), and a prostate about 3 times normal size, which was elastic and did not suggest carcinoma. The following day he became comatose and was kept in bed with an indwelling urethral catheter during the remainder of his stay in the hospital. The blood urea gradually rose until it reached 176 mg. per 100 cc. on October 3, 1938. The patient died the next day in uremia.

Pathology (No. 16069): Autopsy revealed benign prostatic hypertrophy, chronic prostatitis, infarcts of the prostate, cardiac hypertrophy, coronary and generalized arteriosclerosis, myocardial scarring, emphysema, lipoid pneumonia of the right lower lobe, adenomata in both kidneys, cyst of the right kidney, polyp of the ileum, adenoma and hyperplasia of the oxyphilic cells of the parathyroid, cystitis cystica, testicular scarring, cortical atrophy of the brain, and encephalomalacia.

The prostate showed marked enlargement of both lateral lobes and on cross section many small adenomata were seen. No infarct was recognized macroscopically. Routine section of the prostate showed a small but well defined and sharply demarcated infarct, 1 cm. in diameter, in the right lateral lobe. Additional sections revealed a second typical infarct, 0.5 cm. in diameter, in another portion of the right lateral lobe. Surrounding both areas of infarction were a few compressed glands and ducts and many small, irregular, solid masses of squamous epithelium (Fig. 5). All of the metaplasia was confined to the margins of the infarcts. The remainder of the prostate showed only typical glandular hyperplasia and a few foci of leucocytic infiltration.

Final Diagnosis: Benign prostatic hypertrophy. Chronic prostatitis. Multiple infarcts of the right lateral lobe. Squamous cell metaplasia.

Case 8. B.U.I. No. 27748. *Clinical Course:* A white man, aged 82, was admitted to the Brady Urological Institute, December 9, 1938, complaining of stones in the bladder. Seventeen years previously a litholapaxy had been done, and 10 years before admission he passed 5 small calculi through the urethra. For 5 months there had been urinary frequency and occasional hematuria. Examination revealed generalized arteriosclerosis, a loud apical systolic murmur, hypertension (200/105), and marked enlargement of the prostate with no suggestion of malignancy. Catheterization revealed 600 cc. of residual urine. X-ray showed

5 large calculi in the bladder and another in the lower left ureter. Intravenous urography showed hydronephrotic kidneys which were functioning poorly. Cystoscopy showed marked intravesical and intraurethral lateral lobe hypertrophy of the prostate and a definite median lobe. On indwelling urethral catheter drainage the blood urea dropped from 80 to 44 mg. per 100 cc., and on December 17, 1938, suprapubic cystolithotomy was carried out under spinal anesthesia. The 5 calculi were removed from the bladder but the stone in the left ureter could not be located. A catheter was introduced into the left renal pelvis and was left in the ureter. The patient had marked postoperative abdominal distension but this was controlled satisfactorily by continuous duodenal suction. Despite abundant intravenous fluids the blood urea rose steadily and reached 132 mg. per 100 cc. on December 24. The next day he developed fever and râles in both lungs. The patient died in uremia on December 25, 1938, with what appeared to be a terminal broncho-pneumonia.

Pathology (No. 16170): Autopsy revealed bilateral hydronephrosis and hydroureter, left ureterolithiasis, benign prostatic hypertrophy, infarct of the prostate, diffuse cystitis, bilateral lobular pneumonia, and generalized arteriosclerosis.

The prostate showed marked enlargement of both lateral lobes. Each one measured 6 x 4 x 4 cm. A large median lobe projected into the bladder for a distance of 3 cm. On cross section both lateral lobes showed many small adenomata. The median lobe presented a homogeneous, firm, white cut surface. Sections of the median lobe showed an infarct 1.4 cm. in diameter, surrounded by islands of squamous epithelium similar to those described in the preceding cases (Fig. 6). There was no invasion of the adjoining tissue and the metaplasia was confined to this area. Both lateral lobes showed only glandular hyperplasia and a few foci of leucocytic infiltration.

Final Diagnosis: Benign prostatic hypertrophy. Chronic prostatitis. Infarct of the median lobe. Squamous cell metaplasia.

DISCUSSION

Irrespective of the true etiology of these prostatic infarcts, all 11 had squamous epithelium along their margins. These changes in morphology certainly represent more than a simple compression of the glandular acini and are best explained on the basis of cellular metaplasia.

Krompecher showed that squamous epithelium may result from metaplasia in the prostate rather than be due to embryonal inclusions or hypothetical malformations. In a detailed study of structures lined by columnar epithelium he concluded that the squamous cells originated from proliferation of the basal cells. He claimed that these undifferentiated cells are morphologically similar to the basal cells of stratified epithelium and are distributed irregularly on the

basement membrane of the mucosa between the cylindric cells. Normally they divide and differentiate into columnar epithelium to replace the lining cells which are injured or desquamated, but under certain conditions they may differentiate into transitional or squamous epithelium.

Experimental studies by Wolbach and Howe have shown that metaplastic changes can be induced in animals by a diet deficient in vitamin A. In none of our cases was there any evidence of metaplasia elsewhere in the body or any history of dietary deficiency.

Metaplasia also occurs in certain areas subject to chronic infection (e.g. bronchial epithelium, bladder, renal pelvis). Although chronic prostatitis was present in many of the cases in the present series, metaplasia occurred only along the margins of the infarcts.

Squamous cell carcinoma may occur in the prostate but is very uncommon and should be diagnosed with great caution. It may be difficult to differentiate between metaplasia and carcinoma in any single metaplastic nest of epithelium, but since metaplasia occurred along the margins of all of the 11 prostatic infarcts in our series, since in none of the cases was there any pathological evidence of spread beyond that area, and since 3 of these patients have been followed for $4\frac{1}{2}$, 7 and 8 years, respectively, without clinical or X-ray evidence of carcinoma, the evidence is decidedly against the malignant nature of the metaplastic areas. Three other patients died from unrelated causes and showed no metastases at autopsy. Another patient had no clinical signs of malignancy at the time of operation and death. The remaining patient in this series is living and well 5 months after operation with no clinical or X-ray evidence of carcinoma.

The causal relationship between metaplasia and the infarcts remains obscure but the fact that the squamous epithelium is limited to the periphery of the infarcted area in each case suggests that the infarction may, in some way, be the precipitating factor.

SUMMARY

Only 1 previous case report of metaplasia in the prostate associated with infarction, has been found in the literature.

Eight cases, presenting a total of 11 typical infarcts of the prostate, were studied and in each instance squamous epithelium was noted

along the periphery of the infarct. In 5 of these cases the cellular changes had been interpreted previously as early carcinoma. The squamous cells in all of the cases were confined to the margins of the infarcts and the remainder of the prostatic tissue in each case showed only typical benign glandular hyperplasia. Four of the patients are living and well, as long as 8 years after prostatectomy, and have no clinical or X-ray evidence of carcinoma. Three patients died from other causes and no metastatic lesions were found at autopsy.

From the evidence presented in this study it seems clear that squamous metaplasia, simulating carcinoma, frequently occurs along the margin of prostatic infarcts. This condition should not be confused with the very rare squamous cell carcinoma of the prostate.

I wish to acknowledge my profound indebtedness to Dr. Arnold R. Rich, Associate Professor of Pathology, Johns Hopkins School of Medicine, for his invaluable aid in completing this study; to Dr. B. S. Abeshouse, Sinai Hospital, for permission to study his previously reported cases, and to Mr. Charles Elvers, Brady Urological Institute, for his excellent illustrations.

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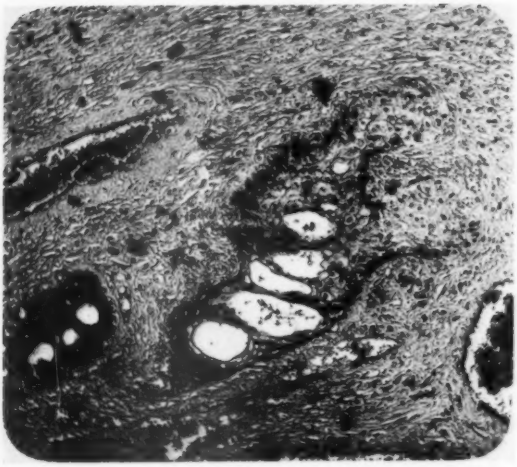

FIG. 1. Low power photomicrograph of an irregular nest of metaplastic squamous cells, simulating carcinoma, along the margin of an infarct (Case 1, right lobe).

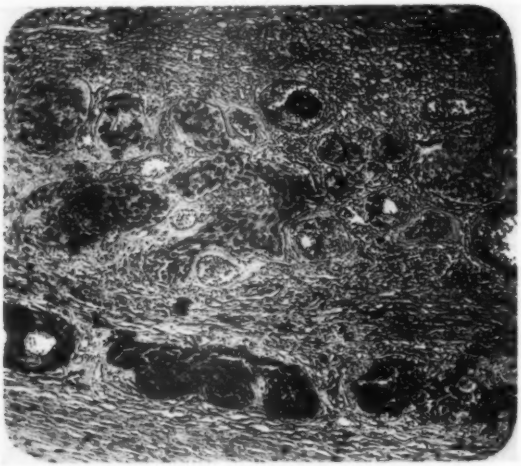

FIG. 2. Low power photomicrograph showing several islands of pale squamous epithelium in the center and darker staining compressed acini toward the bottom (Case 1, left lobe).

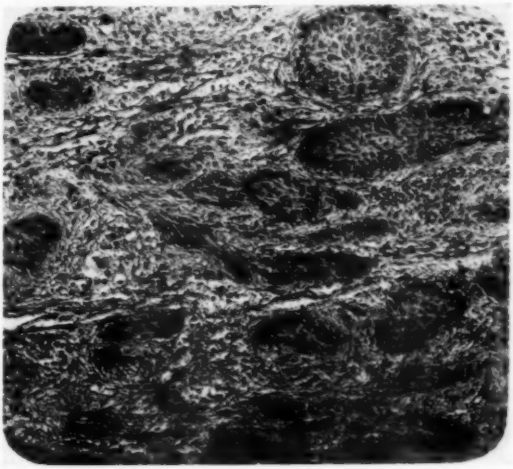

FIG. 3. Low power photomicrograph of the periphery of an infarct showing many irregular accumulations of metaplastic squamous epithelium resembling carcinoma (Case 2).

FIG. 4. Low power photomicrograph showing a central island of squamous and transitional epithelium, a zone of infarcted tissue at the top, and relatively normal prostatic stroma at the bottom (Case 6).

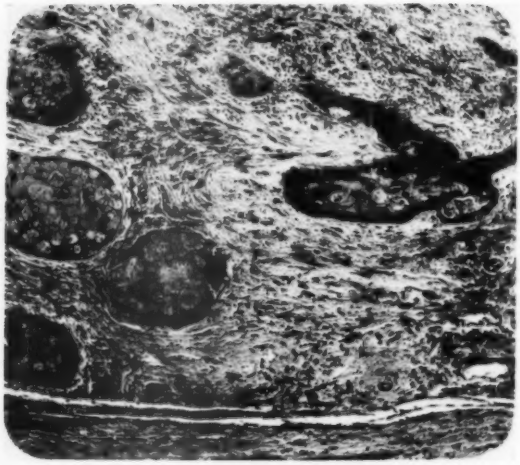

FIG. 5. Low power photomicrograph of the margin of an infarct showing several nests of squamous cells, with suggestive invasion of the adjoining stroma at the bottom (Case 6).

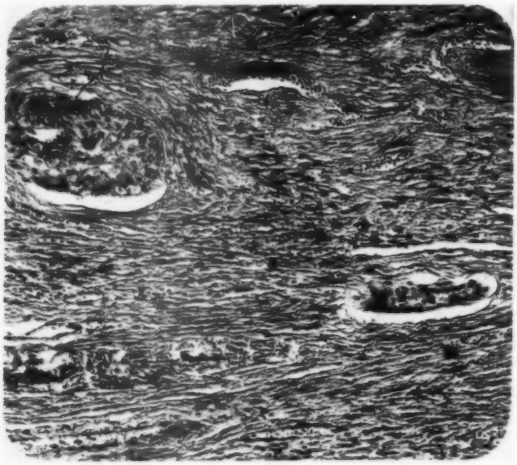

FIG. 6. Low power photomicrograph showing 2 small islands of metaplastic squamous epithelium along the margin of an infarct (Case 8).

CHEMICAL REACTIONS OF NICOTINIC ACID AMIDE IN VIVO[1]

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Nicotinic acid in the form of trigonellin has been known for some fifty years to be a constituent of plants (19). The recognition of its importance in the animal economy is, however, a matter of recent years. We owe its classification as a vitamin to the work of Elvehjem and his coworkers (10) who demonstrated its curative action in cases of canine black tongue; and to Fouts (17) and Spies (37) and their collaborators, and others, for their work on human pellagrins. However, as is true of most of the vitamins of the B group, our knowledge of the function of nicotinic acid amide in biological processes has developed concomitantly from dietary deficiency studies on the one side and from the isolation of substances important to biological oxidations on the other. It is with the rôle in biological oxidations of compounds containing nicotinic acid amide that this review will deal.

The participation of nicotinic acid amide itself in normal biological processes has, as far as I am aware, not been demonstrated. It functions apparently only in such processes after it is incorporated with other building stones into compounds that we may classify as dinucleotides. The rapid synthesis of these dinucleotides in the human body after the administration of nicotinic acid to pellagrins has been demonstrated by Kohn (21) and by Vilter and others (39). Two such compounds are known. The first one to be isolated was obtained from red blood cells in Warburg's laboratory in 1935 (44); it contains one nicotinic acid amide group, one adenine, two pentose, and three phos-

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phoric acid groups. The other, isolated a year or so later in both Warburg's (42) and von Euler's (15) laboratories, contains the same units less one phosphoric acid group (see fig. 1). The exact structural formula for these two compounds is not known. From the evidence available it appears that we are dealing with two mononucleotide units which are linked together in some manner through the phosphoric acid groups. I shall not enter into a further discussion of the structure here, but shall refer to these two compounds in what follows as diphosphopyridine nucleotide and triphosphopyridine nucleotide.

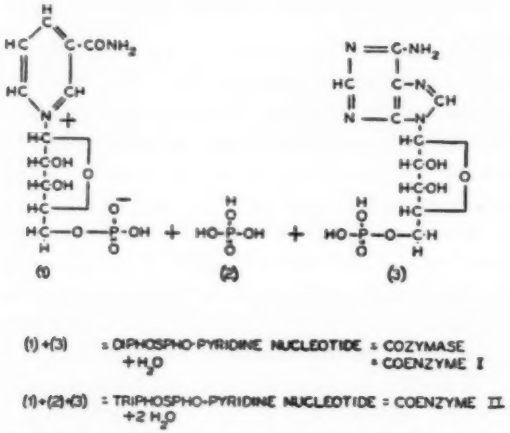

FIG. 1. THE COMPOSITION OF THE PYRIDINE NUCLEOTIDES

Warburg's second important contribution in this field was made when he and his coworkers (44) were able to show that triphosphopyridine nucleotide constituted a reversible oxidation-reduction system and that the nicotinic acid amide part was what we may call the functional group in the process. If we abbreviate the formula to show only the groups concerned, we may represent the reversible oxidation-reduction reaction as shown in figure 2. Reduction occurs at the carbon-nitrogen linkage in the pyridine ring, the quaternary nitrogen disappearing. Also portrayed here are the absorption spectra of the oxidized and reduced forms. As may be seen, the reduced form possesses a characteristic band at λ 340 mμ which is not present

in the oxidized species. Diphosphopyridine nucleotide behaves in a similar manner (cf. Warburg (40)). This difference in the absorption spectra of the oxidized and reduced forms of the pyridine nucleotides has been of inestimable value in following their participation in biological reactions.

A characteristic example of the rôle of the pyridine nucleotides in biological oxidation is the system which led Warburg, Christian, and Griese (44) to the discovery of the triphosphopyridine nucleotide. Here the substrate to be oxidized is hexose monophosphate and the

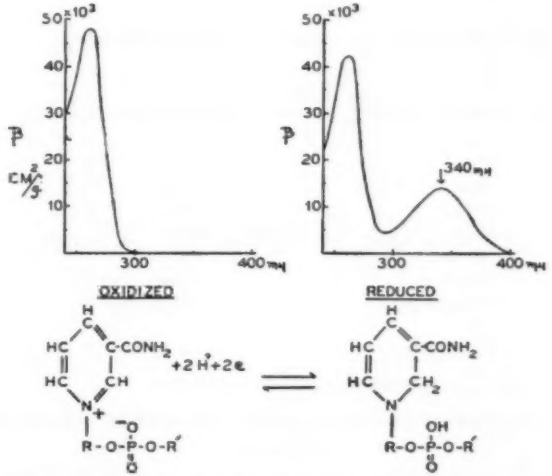

FIG. 2. DIFFERENCE IN ABSORPTION SPECTRA AND CHEMICAL STRUCTURE OF THE OXIDIZED AND REDUCED PYRIDINE NUCLEOTIDES

oxidizing agent is oxygen. If we symbolize triphosphopyridine nucleotide as $Py(PO_4)_3$—then the first step of the reaction may be represented as the oxidation of the aldehyde group of the sugar to an acid group and concomitant reduction of the pyridine nucleotide (see fig. 3). The reaction is dependent on the presence of a specific protein obtainable from red blood cells or yeast, which functions by uniting with both substrate and pyridine nucleotide. The reduced pyridine nucleotide is not oxidized by air. This fact led Warburg and Christian (41) to the discovery of a new class of compounds—the

flavoproteins. The one symbolized here is capable of oxidizing the reduced triphosphopyridine nucleotide and thus regenerating it for another cycle. The reduced flavoprotein so formed is oxidizable by oxygen. Thus it also is regenerated and can react in a cyclic fashion. The overall result is the oxidation of the hexose monophosphate by oxygen, producing a phosphohexonic acid. This in turn may be further oxidized by oxygen with the help of the triphosphopyridine nucleotide and flavoprotein cycle if further protein additions are made. Attempts to substitute the diphosphopyridine compound in any of these reactions lead to failure.

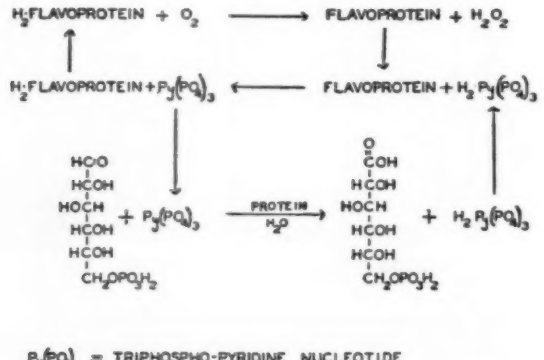

FIG. 3. THE RÔLE OF TRIPHOSPHOPYRIDINE NUCLEOTIDE IN CARBOHYDRATE OXIDATION

Wherever the pyridine nucleotides enter into the cycle of a biological oxidation they apparently function in a manner similar to that depicted here. They react with the substrate only in the presence of a specific protein, their union with this protein being a loose one so that a constant coupling and uncoupling is always occurring. If oxygen is to enter the cycle then a flavoprotein must be present to function in the manner here portrayed.

Though the diphosphopyridine nucleotide is inactive in the carbohydrate oxidation depicted above, it is, however, active in another set of reactions in which hexose diphosphate is the substrate. This chain of reactions is shown in figure 4. In order to facilitate the

presentation each reaction has been numbered, and the data pertinent to it, along with author references, have been assembled in Table I. Here the substrate, hexose diphosphate, first undergoes an enzymatic fission as shown in reaction 1 whereby two phosphorylated triose molecules are produced. They can be converted one into the other in the presence of a suitable enzyme as indicated by reaction 2. All three compounds are apparently in equilibrium in muscle *brei*, the

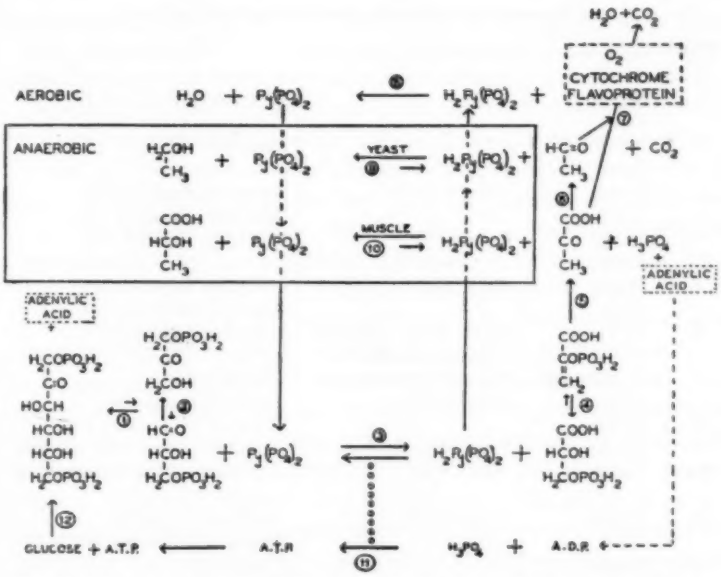

FIG. 4. THE RÔLE OF DIPHOSPHOPYRIDINE NUCLEOTIDE IN CARBOHYDRATE OXIDATION

equilibrium state being indicated roughly in the diagram by the length of the arrows. One of the triose molecules, presumably the aldehyde form, now reacts with the pyridine nucleotide in the presence of a specific protein (reaction 3). As in the previous scheme the pyridine nucleotide is reduced, while an acid is produced. Here the reduced pyridine nucleotide may be reoxidized by oxygen only through a flavoprotein cytochrome chain, as represented in reaction 8, and so

reenter the cycle. The flavoprotein is not identical with that represented in figure 3. The phosphoglyceric acid formed may undergo a series of enzymatic rearrangements (reaction 4) which produces phosphopyruvic acid. This in turn may decompose in the presence of adenylic acid into pyruvic acid (reaction 5). We will return to the fate of the PO_4 radical shortly. The pyruvic acid may then be fur-

TABLE I

Supplementary data concerning the reactions shown in figure 4

REACTION	ENZYME SOURCE	FACTORS AFFECTING REACTION*	REFERENCES†
1	Muscle		Meyerhof, Lohmann (31)
	Yeast		
2	Muscle		Meyerhof, Kiessling (27)
	Yeast		
3	Muscle	Iodoacetate (I)	Meyerhof, Kiessling (28)
	Yeast		Meyerhof, Ohlmeyer (32)
4	Muscle	Fluoride (I)	Meyerhof, Kiessling (26)
	Yeast		
5	Muscle	Mg^{++} (A)	Lohmann, Meyerhof (24)
	Yeast		Meyerhof, Kiessling (29)
6	Yeast	Mg^{++}, Mn^{++} and Diphosphothiamine (A)	Lohmann, Schuster (25)
7	B. Delbruckii	Diphosphothiamine (A)	Lipmann (23)
	Brain, etc.	Fluoride (I)	Barron, Lymann (5)
8	Muscle		Straub, Corran, Green (38)
9	Yeast	Iodoacetate (I)	von Euler, Adler, Hellström (14)
10	Muscle		von Euler, Adler, Günther, Hellström (13)
11	Muscle	Arsenate (I)	Needham, Pillai (34)
	Yeast		Meyerhof, Ohlmeyer, Möhle (33)
12	Yeast		Parnas (36)

* (I) = Inhibitor. (A) = Accelerator.

† See also Table II.

ther oxidized, with the aid of diphosphothiamine and the flavoprotein-cytochrome-oxygen systems, to CO_2 and H_2O (reaction 7). Thus the carbohydrate in the presence of O_2 may be oxidized completely to CO_2 and H_2O; and the pyridine nucleotide undergoes a cycle of oxidation and reduction, and participates over and over again in the primary reaction 3.

Observe, however, what may happen if the supply of oxygen is cut

off. The reoxidation of the reduced pyridine compound by oxygen is now no longer possible. The primary reaction 3 therefore should come to a standstill due to the depletion of the oxidized pyridine compound which is, of course, present in small quantities in comparison to the substrate. However, the pyruvic acid formed will also now no longer be removed and therefore another reaction may occur. This is the oxidation of the reduced pyridine nucleotide by pyruvic acid yielding lactic acid and regenerating the pyridine nucleotide for the primary reaction, as shown in reaction 10. Breakdown of carbohydrate, anaerobically, to lactic acid will then proceed until equilibrium conditions or acid formation call a halt to the process.

In yeast a similar reaction may occur. Here, however, the pyruvic acid is first decarboxylated by means of diphosphothiamine and a specific protein to form aldehyde and CO_2 (reaction 6). In the absence of oxygen the aldehyde reoxidizes the pyridine nucleotide and is in turn reduced to alcohol (reaction 9). The carbohydrate breakdown then proceeds in a manner analogous to that in muscle except that alcohol and CO_2 are produced instead of lactic acid. By the production of CO_2 by the carboxylase reaction yeast tends to shut off its oxygen supply and thus establishes an anaerobic existence.

In this diagram I have, rightly or wrongly, depending on your viewpoint, placed the emphasis on the rôle of the pyridine nucleotide, rather than on the substrates. In so doing, however, I think that perhaps one can obtain a clearer insight into the so-called Pasteur effect. The Pasteur effect is usually defined as the action of oxygen on living cells which reduces the rate of carbohydrate destruction and suppresses or diminishes the accumulation of the products of anaerobic metabolism (cf. Dixon (8)). The chief products of anaerobic metabolism are recognized as lactic acid and alcohol. How oxygen suppresses the accumulation of these products, is obvious from the relationships here portrayed. The action of oxygen in reducing the rate of carbohydrate destruction must, I think, be sought in the fact that the aerobic process by its complete combustion makes available the total energy of the carbohydrate molecule. The anaerobic process on the other hand by its incomplete combustion liberates only a small part of the available energy of the carbohydrate. Hence to furnish the same amount of energy the rate of carbohydrate disappearance

must be greater under anaerobic conditions than when oxygen is present.

The dephosphorylation of phosphopyruvic acid that occurs in reaction 5 is apparently dependent on adenylic acid as a phosphate acceptor. In this way adenosine diphosphate (A.D.P.) is formed. Now this compound can be apparently further phosphorylated by inorganic phosphate if concomitantly there occurs the oxidation-reduction reaction 3. It appears as if the energy of the oxidation-reduction reaction was utilized in the phosphorylation process. In fact the oxidation-reduction reaction apparently proceeds rapidly only if it is coupled with such a phosphorylation process. The adenosine triphosphate (A.T.P.) so formed may then phosphorylate glucose and thus replenish the substrate hexosediphosphate. [Compare also the phosphorylation of thiamine as presented by Dr. Elvehjem at this symposium and the phosphorylation of glycogen in muscle, Parnas (36)].

The pyridine nucleotides play a rôle not only in carbohydrate oxidation but also in protein metabolism. The work of von Euler and his collaborators (12) has shown that the oxidation of glutamic acid is dependent on the pyridine nucleotides. The mechanism of their action in the oxidation of this amino acid is identical with that encountered in their oxidation of carbohydrate. As shown in figure 5, reaction 1, the pyridine nucleotide in the presence of a specific protein oxidizes the amino group of glutamic acid to an imino group and is in turn reduced. The reduced pyridine nucleotide may now be oxidized, as described before, by oxygen acting through the flavoprotein-cytochrome system (reaction 2) and so reenter the primary reaction. The imino acid formed may undergo a further enzymatic reaction, involving the elements of water, to produce the corresponding keto acid and ammonia (reaction 3).

Amino acids other than glutamic acid are apparently not oxidized by the pyridine nucleotides and in fact only glutamic acid, belonging to the L family, is so attacked. Other amino acids of the L family may, however, undergo what may be termed an indirect oxidation by the pyridine nucleotides by means of the Braunstein-Kritzman (6) transamination reaction 4. In this reaction the keto glutaric acid produced by reaction 3 may react in the presence of a suitable enzyme

with another amino acid of the L family so that glutamic acid is regenerated and the corresponding keto acid of the reacting amino acid is produced. The glutamic acid formed may then, of course, react again by way of reaction 1, etc.

Amino acids belonging to the D family are oxidized by another enzymatic pathway first discovered by Krebs (22). Warburg and Christian (43) have recently shown that the enzyme responsible for this reaction 5 is a flavoprotein, not identical, however, with the flavoprotein operating in reaction 2. Since a keto acid is also produced in

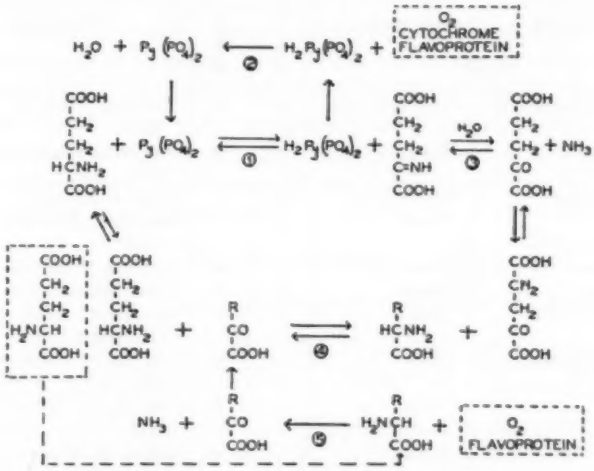

FIG. 5. THE OXIDATION OF AMINO ACIDS

this oxidation the D family of amino acids are thus linked to reaction 4 and hence to the cycle as a whole.

As to whether only glutamic acid of the L series is produced by reaction 4, I have been able to find no conclusive answer. If the unnatural glutamic acid should be formed it cannot be oxidized as stated above by the pyridine nucleotide in reaction 1. It must reenter the cycle through the flavoprotein enzyme oxidation of reaction 5, as indicated by the dotted line in figure 5. The recent finding of Kögl and Erxleben (20) that malignant tumors contain a high percentage of this form of glutamic acid is of interest in this connection.

As will be noted in figure 5, reactions 1, 3 and 4 are reversible. This means that not only the breakdown of amino acids but also their synthesis may follow these pathways. In this connection it is, therefore, of interest to note that protein and carbohydrate metabolism may not only be linked through a common intermediate product, e.g., pyruvic acid, but also through the pyridine nucleotides. Reduced

TABLE II

Substrates oxidized by means of the pyridine nucleotides

SUBSTRATE	ENZYME SOURCE	COENZYME		REFERENCES
		$Py(PO_4)_2$	$Py(PO_4)_3$	
Hexose mono PO_4	Red blood cells	−	+	Warburg, Christian, Griese (44)
	Yeast	−	+	Warburg, Christian, Griese (44)
Triose PO_4	Muscle	+	−	Adler, Günther (2)
	Yeast	+	−	Meyerhof, Kiessling, Schulz (30)
Alcohol	Yeast	+	−	Negelein, Wulff (35)
Lactate	Muscle	+	−	Adler, Michaelis (4)
Glycerol PO_4	Muscle	+	−	von Euler, Adler, Günther, Hellström (13)
Glutamic acid	Liver	+	+	von Euler, Adler, Günther, Das (12)
	Yeast	−	+	von Euler, Adler, Eriksen (11)
	B. Coli	−	+	Adler, Hellström, Günther, von Euler (3)
	Plants	+	−	Adler, Das, von Euler, Heyman (1)
Glucose	Liver	+	+	Das (7)
Aldehyde (Mutase)	Liver	+	−	Dixon, Lutwak-Mann (9)
β-hydroxybutyrate	Muscle	+	−	Green, Dewan, Leloir (18)
Malate	Muscle	+	−	Adler, Michaelis (4)

pyridine nucleotides produced in the carbohydrate cycle may well enter into reaction 1 so as to affect amino acid synthesis especially under anaerobic conditions.

It is of interest that the oxidation of glutamic acid proceeds through either the diphospho- or triphosphopyridine nucleotides if liver is the source of the enzyme (12). As shown in Table II, the oxidation of

glutamic acid in other cells proceeds through one or the other but not both. Also shown in Table II are other substrates whose oxidation is dependent on the pyridine nucleotides; these cannot be considered here.

In conclusion, therefore, we may say that the pyridine nucleotides constitute reversible oxidation-reduction systems whose functional group is nicotinic acid amide. In combination with specific proteins these reversible oxidation-reduction systems play a central rôle in the initial reactions by which carbohydrates and amino acids undergo oxidation and synthesis in the animal organism. These initial reactions however, in which the pyridine nucleotides play a cyclic rôle, are dependent on secondary reactions in which, among other factors, flavoprotein and cocarboxylase play an important part. It is thus obvious that at least three vitamins of the B group, thiamine, riboflavin, and nicotinic acid, are collectively concerned in biological oxidations and that any investigation of the rôle of one of these demands a consideration of the other two.

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RELATION OF PSYCHIATRY TO INTERNAL MEDICINE

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In recent years, internal medicine seems to have been in the process of rediscovering psychiatry. In a number of hospitals there is now a full-time psychiatrist on the medical staff contributing his share to the understanding and treatment of an increasing range of medical problems. Sometimes he works as an internist, sometimes as liaison officer, sometimes frankly as attending psychiatrist. This evolution in internal medicine points to a worth while re-awakening in the internist of a desire to know more about the person as well as the disease with which he is so frequently confronted. The internist of the past, with his preference for laboratory investigation, too often pushed into the background his curiosity about how the patient functions and lives as a total individual. The psychiatrist, meanwhile, partly because of his zeal in research in general medicine, and partly because of his continued interest in the field which gave him his pre-psychiatric training, has slowly but certainly given proof that the contributions of his specialty to the general range of medical practice are of value. The old-time family practitioner, now growing somewhat obsolete, gave something to his patient that the specialist now recognizes as important; namely, a wisdom about the person, his background, his problems—the understanding and management of which constituted part of the practitioner's therapy. When Cannon took emotions into the laboratory, the subject became "scientific." Since then a considerable body of physiological and anatomical facts have accrued concerning the rôle of the thalamus as a primitive receptive center. The clinical researches of Head and Holmes on the thalamus as the organ of feeling, the work of Goltz and Bard on decorticate affective reactions, and a growing body of knowledge concerning the function of the autonomic nervous system and the endocrine glands, have un-

questionably contributed to the internist's growing interest in the general study of emotions.

One wonders why man ever was split into indivisible components, or why medicine was permitted to take only the body and the psychiatrist only that intangible realm of "the mind." The psychiatrist realizes that "a mind" never exists alone or isolated, that it belongs to a person who can never be arbitrarily divided into such simple components. Knowing that he must work with everything that constitutes man, the psychiatrist from the beginning had to acquaint himself with the best available knowledge about physiology, chemistry, pharmacology and internal medicine. As he learned more about the complex interaction of all these components, he began to feel that those physicians who dealt with a detached body failed to appreciate the full range of possible functions of the special organs which he proposed to treat. The internist has come to accept the psychiatrist also as a physician and is availing himself, more and more, of the psychiatrist's contribution as his awareness of the vast rôle of interacting personality and somatic interrelations grows.

Psychiatry has always needed internal medicine. Today many internists frankly acknowledge their indebtedness to psychiatry, which is often able to throw the best light on some of the baffling problems of internal medicine. The wise physician no longer dismisses his psychoneurotic patients who, by conservative estimate, constitute 40 per cent of his practice, nor does he wish to trust to intuition and untrained common sense. Patients themselves are demanding special enlightenment and the best that science has to offer.

The psychiatrist has no desire to take from the internist any of these patients which the internist wants to manage. Both would effect a greater percentage of recoveries, however, by a joint working program whereby the two specialties can share the best of their skill and knowledge. The psychiatrist who has the opportunity of working in a general medical hospital sees an unusual variety and range of these interrelated problems.

THE PSYCHOTIC GROUP

A large group of such patients consists of individuals who are frankly psychotic. Sometimes the psychosis is unrecognized at the time of

admission to the hospital, sometimes it develops subsequent to admission. In some it is clearly an emergency situation; in others, a development of the specific complaints really represents part of the symptomatology of the psychosis; in others, the onset of psychosis makes it difficult or even impossible to carry out necessary medical or surgical therapy. Thus we have seen cases which were clearly examples of manic excitement, depressions of various types, schizophrenias, confusional psychoses, and various delirious conditions. Delirium may develop and complicate many medical issues and has to be prepared for in such conditions as cardiac failure, uremia, pneumonia, infections, pellagra, and in cases of too aggressive drug therapy. Epilepsy and post-epileptic confusional states are not uncommon. An unrecognized alcoholic may develop full-fledged delirium tremens shortly after operation, in which state he may do serious damage to himself or to the surgeon's efforts. Postoperative and postpartum psychoses may constitute dangerous reactions, not alone to the patient but to other patients and to hospital personnel. Patients who constitute suicidal risk must always be recognized and given adequate protection. Never a week goes by in the accident room without some patient being brought in following suicidal attempt. Not all of these need be hospitalized but a decision has to be reached by someone trained to evaluate the severity of the risk. Suicide occurring in hospital may leave the hospital open to legal suit. Frequently a reactive depression to the knowledge of chronic or disabling illness may develop in the hospital, with a resultant protraction of the convalescent period. Unwise nursing or hospital management may contribute to the development of confusional states and psychoses in senile, feebleminded, superstitious or distrustful and insecure patients. Panic reactions may ensue from bandaging of both eyes, from idiosyncrasy to drugs, from unwise research investigations, from discussion by staff members during ward rounds of differential possibilities and prognosis, etc.

THE SO-CALLED "FUNCTIONAL" GROUP

There are personality difficulties which every internist is easily able to recognize and for which he freely asks help. A much larger group of cases constitutes problems in which the psychiatric aspect is

not always immediately evident. In these cases the internist may proceed for a long while with a conviction that he is dealing with a true medical disease, only to find that his therapeutic program is not proving effective or that the patient continues to complain after all reasonable medical factors have been eliminated. The range of problems here falls roughly into four groups:

1) Problems of differential diagnosis. A picture of apparent hyperthyroidism may be produced by severe anxiety states. Chest complaints of pain, dyspnoea, palpitation may be entirely psychogenic in origin but may be difficult to differentiate from angina pectoris or other forms of cardiovascular disease. Headache and vertigo may be purely psychogenic, however strongly suggestive of Meniere's disease or brain tumor. Pseudo-paralyses, anaesthesias, etc. may suggest hemiplegia, although purely hysterical in origin.

2) Actual organic disease may exist but, for various personality reasons, prove unresponsive to therapy.

A 43-year old hypertensive with blood pressure consistently elevated to 198/132 was found to be in a state of depression, tension, anxiety about business, and within ten days of active discussion and modification of the life situations was entirely symptom-free. With management of the obvious emotional component in the illness, his blood pressure two months later had dropped to 148/96.

3) A few patients realize quite clearly the true psychogenic origin or contribution to their symptoms and frankly ask the managing physician for psychiatric help or its equivalent.

A 35-year old man entered the medical division with attacks of palpitation, trembling, dry mouth, and fear that he was going to die. His was a condition of anxiety which he clearly recognized. There was found a mild accompanying elevation of blood pressure, but the patient insisted on transfer to the psychiatric division for treatment of the fundamental personality upset.

4) The largest group of all consists of individuals with physical complaints for which no adequate organic cause can be ascertained. These are the cases most likely to be diagnosed hypochondriasis or neurasthenia, and are either confronted with the statement that they are organically sound and not in need of further medical attention, or are subjected to the traditional rest-cure method of therapy which is not only ineffectual but often harmful. The following patient put in

the foreground her complaints of exhaustion and diarrhea. Since she was not asked about any other factors in her life she did not volunteer the obvious story which gave the clue to her condition.

A 44-year old married woman entered the medical service complaining of diarrhea, attacks of fever, complete exhaustion of three years' duration, unrelieved by a year of thyroid medication. Physical examination was quite negative. To the psychiatrist she complained primarily of trembling and shaking, irritability, brooding, restlessness, and stated frankly that she knew her symptoms had no relation to her attacks of fever and were dependent entirely upon the situation of her unhappy marriage.

She never loved her husband and married him only because she felt flattered by the conquest. Sex relations had always been distasteful to her. For ten years she had been desperately in love with another man but felt she could not divorce her husband because she valued his material support and felt the children needed the security of an undivided home. Her husband was frantically jealous of her. She had dropped out of all social activities; she hated the small community in which she lived; she bemoaned the loss of her former beauty; she felt that her life was over and that the future was empty and dreary. These were the real factors responsible for her profound exhaustion and bedridden invalidism.

The obvious therapeutic program required a complete re-orientation in her mode of life with increase in activities to make up for the deficits in her own marriage. The referring physician sent her home in the care of a nurse for a three months' rest-cure in bed. The patient wrote a frantic letter protesting the therapeutic recommendation which her husband insisted on carrying out.

MEDICAL SITUATIONS IN WHICH THE "PERSON" CAN NO LONGER BE EXCLUDED

It must be evident from this general introduction that the internist has a responsibility to recognize and deal with the human personality. These are the cases in which the internist must obligate himself to inquire into the whole range of human functioning. If he neglects to do so, he fails to do justice not only to the patient but to his own best clinical usefulness. The psychiatrist can here make himself an integral member of the medical profession when, with his special training, he is able to obtain or to clarify the pertinent psychogenic factors.

Let us now consider in detail this special group of patients where the problem is not specifically psychiatric and where the joint cooperation of internist and psychiatrist brings the best results. This is the large group of patients who, by preference, go first to the internist

because they have a specific complaint or complaints for which they want help. The internist is likely to include the entire group under the general heading of psychoneurosis, particularly when exhaustive medical search reveals no adequate basis for the patient's complaint. These are the patients who go to many doctors and who are often pathetically confused by the conflicting statements, diagnoses and advice they have received. They are often not helped by the usual medical procedures and may be made worse by unwise management. The physician may recognize the complaints as clearly mental when the patient speaks of troublesome obsessive thoughts, compulsions to perform certain actions, fears which he recognizes are unwarranted, or when he is mistakenly convinced that he is suffering from dire disease which physicians have not been able to find. More often the patient feels no responsibility for such symptoms as tearfulness, tremulousness, despondency, anxiety, exhaustion, multiple discomforts, hypochondriacal aches and pains, hysterical palsies, anaesthesias, aphonias, etc. Another group of patients, complaining of palpitation, sweating, globus, vertigo, tension, gastro-intestinal irregularities, motor spasms, and cramps, may be convinced that they have a fundamental disease but still spontaneously recognize that worry, disappointment, anticipation and many other life factors aggravate their symptoms. Occasionally they speak of their symptoms as "nervous stomach," "nervous heart," etc. A fourth group presents a picture so characteristic of well-known medical syndromes that only after joint psychiatric and medical investigation and therapy can it be definitely established whether we deal with pseudo-angina, pseudo-Meniere's, pseudo-Graves disease, etc.

CASES THAT EVERY INTERNIST SHOULD BE ABLE TO MANAGE ALONE

A large group of such patients, constituting states of simple depression, anxiety, neurasthenia, hypochondriasis and functional alterations in the physiological status present problems which the internist is able to manage alone. These are cases in which even the most cursory attention to the life situation of the person reveals facts so startling that the essential nature of the condition becomes immediately obvious, and where management of the life situation, attention to the balancing of work, recreation, play and sleep bring

immediate relief. Any such patient, in an hour's planned conversation, will give the physician facts which permit him easily to recognize and deal with the pertinent situational conditions. The following two cases will illustrate how any internist by a brief review of the personal factors in the life of his patient can easily make clear the true nature of the condition.

A 39-year old married woman lawyer came to the Diagnostic Clinic October 24, 1938, complaining of creepy sensations in her spine, feeling alternately hot and cold, of tremulousness, and stating frankly that she might be imagining some of her symptoms and that much of her trouble was connected with nervousness. Physical examination revealed only back strain and an otosclerosis producing increasing deafness.

She stated that for several months she had been increasingly tremulous, jittery, inefficient at work and had noticed poor memory and concentration, early morning awakening, easy tearfulness, heavy head sensations and restlessness.

She readily told her story which gave the clue to her condition. When 19, she married a young lawyer and entered law school so that she might keep pace with him. She was extremely successful and, as head of a research division, had to keep ahead of several brilliant young law graduates. Two years after her marriage, her husband had encephalitis and was unable to do any further work. For the past three years he had been hospitalized with a paranoid psychosis. She had tried repeatedly having him at home but his behavior was disturbing to everyone in the house. He had four times instituted legal proceedings for release from hospital. For eight years, therefore, this woman had supported herself and three children. The oldest, a boy, was in college, adjusting poorly, interested in radical labor movements to the exclusion of studies. She had two boarders in the house to help out financially. She was unable to get adequate help. She spent her Saturday afternoon off shopping, and every Sunday at the psychiatric hospital with her husband. Growing deafness made social contacts a strain, and theatres, music and movies, which she once loved, were impossible. In this setting she had become increasingly tense, finding a little relief in warm baths. At the time of examination she was in a mild depression with marked tension, which adequately accounted for her symptoms.

In the preceding case, the facts poured themselves out. It was necessary only to scrutinize her complaints in the broader setting of her life and to look for experiences in her life which were clearly precipitating factors. Common sense demands that these facts be included in the formulation of this woman's medical situation. Her condition could never satisfactorily be explained by search for foci of infection or irregularities in one or another organ or gland. The

psychiatrist's rôle in such a case is to give the medical man a chronological account of the life, the development of the problems and situations and the correlation of the onset of the symptoms with specific events of the life story. A description of the patient's personality and constitution enables us to understand what the symptoms meant to the patient herself.

The facts thus elicited, particularly when they coincide chronologically with the development of the symptoms, will be easily appreciated as etiological factors, not alone by the physician but often quite spontaneously by the patient.

In the next case the patient had already recognized this relationship.

A 40-year old married insurance salesman entered the medical service November 29, 1936, complaining of epigastric discomfort and weight loss. For a month and a half he had had burning pain in the right lower quadrant, a great deal of gas, hyperacidity, mucus in the stools. To a medical man he said he had been under nervous and mental strain.

To the psychiatrist he gave a frank statement that most of his troubles were due to worry. He had an amazing story of maladjustment in almost every sphere of his life. He worked under high pressure, constant interruptions, and had a superior with whom he did not get along. The other men in the office complained to him but he was unable to modify the situation. For ten years he had been having gastro-intestinal discomfort with alternating diarrhea and constipation. He was finicky about food, feared eating and "ulcer."

From earliest life he was timid, insecure, lacking in confidence and stuttered until 16. He never got on well with his father who was a heavy drinker. He went to work early to help support his family. He was constantly worried about an older brother, a ne'er-do-well who gambled and stole, and whose problems he had frequently had to untangle. He married at 22 and had three boys who constantly quarreled among themselves. He had dreaded having any more children. Because of fear of masturbation in his own early life he was overconcerned about its occurrence in his children. He had never been able to save money and lived from day to day. Gradually the family had lost contact with all its friends. He got practically no recreation. In temperament he was overly sensitive, overly conscientious, unsociable, lacked confidence in his abilities, had a rigid code, was tense and striving.

In view of his completely negative physical examination, aside from a mildly spastic intestinal tract, he was spontaneously able to account for his symptoms on the basis of his tense condition and to accept the need for modification in his life as the essential therapy.

CASES IN WHICH ONE PSYCHIATRIC CONFERENCE MAY CLARIFY THE ISSUE FOR THE INTERNIST

Sometimes, however, the personality facts are not so clearly evident, and a certain skill in obtaining the history is necessary before the correlation between the events of the life and the onset of the symptoms becomes evident. The psychiatrist can often, in a single interview, clarify the problem sufficiently to enable the internist to carry on with more profitable understanding. In the following case, the patient herself had a very unclear awareness of the rôle of her troubled life in the production of her symptoms. Once this was brought to light and she was able to see chronologically, through the years, the definite dependence of symptoms upon events, she quickly accepted the explanation and with this new insight and with the help of her internist she was able to overcome her difficulties.

A 28-year old married employed woman entered the medical service March 19, 1937, complaining of exhaustion and fatigue of 3½ years' duration. Her first physician suggested that she had anemia and gave her liver and iron. Following a promotion at work her symptoms were worse. Her physician then found a B.M.R. of −21 and began thyroid extract with some temporary improvement in her exhaustion. During five years she lost from 125 to 105 pounds, in spite of being hungry all the time. Thorough medical examination revealed no organic disease and the case was diagnosed *malnutrition*.

To the psychiatrist she gave a very different account with a history of four years' difficulties with four well-marked periods of depression. She was in a phase of definite depression at the time of the examination, complaining of fatigue, low spirits, tearfulness, difficulty in falling asleep, poor concentration, restlessness, irritability and conviction that life was not worth while. She felt best in the evening, worse on awakening.

Her episodes of exhaustion, which really represented depressions, were clearly motivated in the events of her life. She was the youngest child, spoiled and lonely; her education was erratic and she changed colleges three times. Prior to meeting her husband she had been desperately in love with a man who was completely attractive to her but who let her down. This coincided with her first slump in 1933. She then married her present husband, but for a year and a half he had been completely impotent, getting prostatic massages and being incapable of sex relations. Throughout her four years of marriage, she resented her ne'er-do-well brother who was supported by the mother, who, in turn, got part of her income from the patient. She continues sending the mother money out of a sense of obligation. She had high ambitions for her own future and for a life of ease,

but was married to a man whose earning capacity was stationary at $2,000 a year. In order to exist with reasonable comfort, she had had to continue work but even then could only afford a two-room apartment and no luxuries. She had to give up her piano study which was her one real interest. She constantly drove her husband to get ahead but he was an unambitious person who, failing in the private practice of law, had settled down to a routine government position. She constantly dreaded that he would bring his mother into their apartment. They went out infrequently and had few recreations. The life chart brought out clearly the correlation between her symptoms and these episodes of strain. She stated quite frankly that all her difficulties were related to periods of emotional upset.

Her husband stated frankly that her ill-health began with their marriage and the attendant difficulties. He agreed to undergo psychiatric treatment for his impotence. Insulin helped the patient to gain weight. With reassurance about her physical status and reorientation of her mode of living, she wrote four months later that she was feeling quite well and had gained ten pounds in weight.

This case indicates how psychiatry can obtain for the internist the pertinent facts which give the clue to the reaction. Such conditions are not always easy to unravel. We may be dealing with a difficult or deep-seated neurosis or a patient who is totally unwilling to face the rôle of his own personality in his symptoms or who, because of sensitiveness or "mind-shyness," proves inaccessible or uncooperative. The average physician, faced with such a patient, may become impatient or resentful of the inroads on his time necessary to get the story, or annoyed because the patient seems so recalcitrant to the acceptance of his negative findings and diagnosis of psychoneurosis. The patient, on his side, resents the diagnosis without the encouragement of treatment for his personality difficulties.

CASES IN WHICH PSYCHIATRIST AND INTERNIST MAY WORK PROFITABLY TOGETHER

There is another large group of patients in which the individual is best served when the psychiatrist and internist jointly carry the program of therapy. The internist need not relinquish his patient and may carry the patient throughout the treatment period, getting help from time to time as he feels the need for it in the understanding and management of the personality issues. The psychiatrist in this situation serves as a consultant who may see the patient from time to time for the investigation of complex or obscure factors, while at the same time the internist is managing the day-by-day therapy. The

following case proved of great interest to the psychiatrist because of the possibility of sharing the therapeutic program with the internist who was, because of his close daily association with the patient, in the best position to carry out the day-by-day management of the problem.

In the fall of 1938, the referring physician asked the psychiatrist for advice prior to the admission to the medical service of a 48-year old married woman who had been under medical care at home for a period of several months. There, under thyroid medication for amenorrhea, she had become increasingly agitated, tearful, careless of her appearance, often thrashing about in bed. It was considered advisable to have admission to the medical service for complete study of the somatic status and for further psychiatric observation of the disturbed behavior.

It was immediately evident on admission that the patient was profoundly depressed and agitated, harping on the ruination of her life—"I have just collapsed. It's all terribly mixed up. I was so stubborn—I brought it all on myself. Now the end has come." She gave a history of having lost weight, of amenorrhea, loss of appetite, miserable sleep, crying spells, conviction that life was no longer worth while. The circumstances preceding the onset of this illness in March 1938 had to do with overwork, financial worry, disappointments in an investment which she had undertaken during a preceding hypomanic phase, responsibility for which she now felt unable to meet.

Thorough physical examination revealed weight loss and spasticity of the gastro-intestinal tract. Otherwise the physical and laboratory findings were completely negative. No neurological basis could be found to explain the numbness and paraesthesias of the legs which accompanied her emotional outbursts.

She was a woman of lifelong ups and downs of mood, self-willed and imperious in her management of her own and her family's life—an individual who, at 48, was faced with the first unmodifiable frustration of her life. The condition was formulated to the internist as an agitated depression and a plan of therapy was jointly mapped out, which included regular occupational therapy, cold wet packs and prolonged baths for relaxation, small doses of barbital during the day and sedative for sleep at night, exclusion of all visitors and relatives, specific medical therapy of progynon twice weekly.

The internist was to see the patient daily, giving her ample opportunity to discuss her complaints, preoccupations and worries. The psychiatrist agreed to see the patient twice a week and, in the course of time, was able to fill in more of the details of the illness and of the previous life. It was clear that the patient was hypomanic in the spring of 1938, overactive and organizing several projects. The patient expressed concern over her daughter's impending marriage, of which she disapproved. She discussed in detail her own unhappy marriage, worry about her mother's health, concern over what her friends would think of her present condition.

Within a month she had shown remarkable improvement, was able to face frankly the financial situation, her own error in getting involved in it and the necessity to assume responsibility and see the situation through. Within two months she was seeing friends, spending part of the day outside of the hospital, had gained weight, was meticulous in appearance. She continued to reiterate her terrible cataclysm to the internist, stating that while she looked cheerful and was able to do more, her fundamental attitude had not altered. She began blaming her physician of last spring for her condition, saying that had she been taken in hand in time, the subsequent developments would never have happened. Repeatedly she turned to the psychiatrist for reassurance about her condition. It was formulated to her as a state of depression from which she would recover. She seemed to accept reassurance. At the end of 2½ months sedatives were discontinued; her sleep was adequate; she had resumed interest in some of her previous activities. She began insisting that she was well enough to leave hospital. The psychiatrist advised a weekend at home which she managed with reasonable success, and, following this period, plans were made to leave hospital.

Throughout the entire hospital period, the internist was able to manage the case and was able to contribute a great deal by his daily visits, his reassurance, his understanding of the total situation and the specific features of the depression. The psychiatrist's rôle consisted in the organization of the plan of treatment, the evaluation of the suicidal risk and its protection by nursing care, formulation of her illness to her, the clarification of the true nature of her complaints, the use of sedatives, therapeutic discussions on the need to accept and face her situation, and the making of plans for her future.

CASES IN WHICH THE PATIENT IS BEST SERVED BY TRANSFER TO THE PSYCHIATRIST

There remains a considerable group of patients where psychiatric skill and experience is imperative for the best management of the case. Such conditions as obsessions, compulsions, serious hysterical illnesses and complicating psychotic conditions had best be taken over by the psychiatrist. The internist without psychiatric training or skill may complicate such cases tremendously, and often it is advisable to have the patient transferred to a psychiatric hospital where the facilities for management of the 24-hour routine are better organized. It seems quite impossible that the following two patients could have been cured without the attention of competently trained psychiatrists.

A 34-year old married woman was referred by her family physician for thorough examination because of attacks of diarrhea and vertigo suggestive of

Meniere's disease. The otolaryngologist found normal hearing, intact sinuses and Eustachian tubes, absence of tinnitis, but a hyperactive vestibular apparatus by caloric test. General physical examination was otherwise negative.

To the psychiatrist she complained of attacks of dizziness of ten years' duration with marked anxiety in definite relation to situations in her life, discomfort in the neck due to tension, lifelong fear of closed spaces. Since general physical, neurological and otological examinations were inconclusive, it was felt advisable to institute psychiatric therapy in hospital to determine what rôle the obvious anxiety component was playing.

Her story, as finally obtained, began ten years previously with an attack of light-headedness, with no sensation of whirling, while attending a meeting in a very hot room. She recovered in two or three minutes. Seven years later the second attack occurred in a large crowd at a wedding. Five years ago she felt dizzy while sitting in a theatre one evening, and had to go home. Ever since then she had had to sit next to the aisles, and had gone to fewer social affairs, fearing attacks of dizziness. The real present illness dated nine months previously when during the serious illness of her husband, she was hurrying with her shopping one day and had a violent attack in which she felt as if she whirled around, as if she were walking up a steep hill. She reeled, was nauseated, could not keep in a straight line and had to sit down on the sidewalk. These sensations continued for four hours and were followed by severe diarrhea for half a day. Her husband's serious cardiac condition lasted several months more, during which she was told he might die at any moment. At the time of entering hospital, she was having attacks every two weeks, was terrified of being left alone, wanted a nurse with her, had given up all athletics and social contacts and was becoming increasingly irritable.

As psychiatric investigation continued, it was evident that if she had pseudo-Meniere's disease, there was also present a marked personality component, since any situation in which she found herself alone resulted immediately in dizziness but no major attacks. In hospital her confidence slowly increased and she began eating in the dining room, participating in gymnasium and dancing classes. Within a few weeks she was able to discharge her private nurse.

The story which finally explained this illness was slowly obtained, but is as follows: The patient, a reticent, proud person, met and married, at 27, a wealthy man eight years her senior, member of a proud and prominent family from another part of the country. Having felt insecure concerning marriage, she welcomed with pride his attentions. On their honeymoon her husband was cold and made no sexual advances. She felt bewildered by this but talked to no one about it. When they returned home, his mother died and, when no sex relations yet occurred, the patient excused her husband on the basis of grief over his mother's death. During the first two years of marriage he showed no emotional interest in her and would never discuss the question of having children. Instead, he did everything he could to humiliate her in public, drank inordinately in order to em-

barrass her and paid her no attention at social affairs. She felt completely abashed, insecure in her home, could not understand her husband's attitude, and he refused to discuss it. She recalled the attack of dizziness in the theatre and related it to humiliating circumstances with her husband. He finally decided to impregnate her, and two children were born. She, who was deeply in love with him, felt herself important to him only because she was the mother of his children. It was during the year of his serious illness and her anxiety about him that her symptoms became well-advanced.

With her consent, we carefully brought up his marriage for discussion with him. It was obvious that he had grown attached to his wife and was anxious to help her. He soon volunteered that he had set out on his marriage to be cruel to her, to have no sex relations with her. His reason for this was that three days before his marriage someone had told him that his fiancée had contraceptive information. He was infuriated, being of the opinion that the first baby should come naturally. He was able to see how his rigid attitude had played the leading rôle in her illness.

It was evident to us that we were dealing with anxiety attacks in a person of extreme tension and insecurity. As the factors became clarified and the marital situation was adjusted, her symptoms entirely disappeared, and she left the hospital 2½ months later, completely recovered.

In this case the analysis of the underlying factors required a considerable length of time and the use of special psychiatric techniques for investigation. The management of the case was best carried out in hospital where the atmosphere of security and encouragement was constantly available and where test situations could be created, designed to bring out the patient's assets and performances. Without careful management the marital situation might have been bungled. As it was, the sensitiveness of both partners was spared.

The second case was even more complex because of the confusing medical and surgical therapeutic procedures which had already been tried without effect. The diagnosis itself was not easy to make and it was only after conference with orthopedist, surgeon and psychiatrist that the decision was reached that psychiatric therapy should be tried to confirm the suspicion of hysteria. The surgeon wanted the patient hypnotized immediately; the psychiatrist asked for a period of study to clarify the factors.

A 22-year old unmarried college girl entered the Surgical Service September 8, 1938, complaining of pain in the right hip and leg and weakness of the right leg of nine months' duration—the aftermath of an operation for appendicitis the year previously. Her gait was grotesque. When thorough examination revealed no

cause for her complaints, a psychiatric condition was suspected and the patient was transferred from the surgical to the psychiatric division. Her gait was obviously hysterical in type.

The background of her condition was slowly brought out and the following story elicited: In November 1937, during her senior year at college, she had an acute appendititis with operation. The wound did not heal well and was probed frequently. She was told she had an excessive formation of blood clots; she wore a dressing until January, 1938. The incision remained tender; the patient worried over it and could not accept reassurance. In January 1938 she was found to have developed a keloid and began protecting her right side while walking. In February 1938 she started to limp and to have pain deep in the right gluteal region. Alcohol injection was tried. She was advised to stay out of school but refused. In April 1938 the keloid was removed but the pain persisted in her thigh and she continued to limp. Her physician forbade her to swim, ride or engage in athletics. During the summer at a lake, she felt herself conspicuous and left out of activities. She disregarded orders, went swimming one day, had a catch in her leg, became very much frightened and succumbed to her family's insistence that she live the life of an invalid. In July the hip was injected with novocain. In August an operation was performed and the iliotibial band cut. When she did not improve, her physician suddenly changed his attitude, told her there was nothing the matter, implied she was malingering and trying to upset her family by her imaginary pain. She became frightened that she would never walk normally and that an active life for her was over. She slept poorly and lost some weight. At this point she was brought to The Johns Hopkins Hospital for further surgical therapy.

Her life until junior year at college was uneventful. At that time, disliking the scientific course she was taking, she complained of headaches and dimness of vision and was taken out of school. Her vision then returned. She was babied considerably in childhood, was in marked contrast to her extremely popular and attractive-looking sister. In school she worried over her work, lost sleep in study, strove for the highest grades. She had had mild attention from boys, had formed deep attachments to girls, had had day-dreams about men who paid her no attention. Throughout life she had participated vigorously in all athletics but had been reserved, stubborn, longing for independence, shy, self-conscious, perfectionistic. Her mother was an over-solicitous, over-protective woman who worried constantly over the children.

Within a few days in psychiatric hospital she was sleeping excellently without sedative, had lost much of her apprehensiveness, became quickly coöperative and had begun to complain less about her pain. Her discomfort was formulated on the basis of muscle strain, thereby saving her self-respect and allaying her concern about the accusation of malingering. Graded exercises quickly resulted in rapid and steady improvement in gait. Discussions brought out her desire for emancipation, particularly from her mother and extreme insecurity along social

lines. As she began to understand the situations in her life which had played their rôle, her own self-confidence grew and, at the time of leaving hospital two months later, she had made complete plans for a job on her own away from the family, had a clear realization of her own assets and how she could build upon them, had decided to give up college. Her limp and pain had entirely disappeared and she considered herself tremendously benefited by the increased understanding of her own nature and problems.

This was evidently a hysterical condition, treatment of which required understanding and skill. Any peremptory or bungling attempts at psychotherapy would probably have driven her more deeply into her hysterical state.

I have chosen this series of cases because they illustrate many aspects of a working relationship between general medicine and psychiatry. An increasing number of internists are anxious to undertake, and are undertaking successfully, the therapy of the psychoneuroses. They should be encouraged to do so. This can be done with safety when they avail themselves of the technical, as well as the common sense procedures developed by the psychiatrist. Both internist and psychiatrist have to deal with specific complaints. An effective working relationship is possible and profitable to both.

SUGGESTIONS FOR A TRULY EFFECTIVE WORKING RELATIONSHIP

The preceding cases should give evidence of the usefulness of an interrelationship between psychiatry and internal medicine. These problems are to be found everywhere—in every general hospital, in every physician's office. The psychiatrist, as a consultant, will become increasingly useful to members of the profession as it becomes aware of the function he is willing and ready to perform.

The psychiatrist who undertakes such a rôle must obviously have had training himself in internal medicine, as well as some background in all the biological sciences. He needs to be a person who has kept in touch with advances in general medicine. None the less, he cannot hope to meet all the medical issues involved and realizes that the internist, with his special skill and training, is the person best equipped to pick up discrepancies between the patient's complaints and the physical findings. He has come to lean heavily on the internist for his help in the management of many somatic aspects of his own psychotic and psychoneurotic cases. When diagnostic issues are unclear, he frequently must rely on the internist's specific findings to settle the

issue. When the psychotherapeutic program is begun, he frequently finds that the internist's thorough physical examination is the cornerstone on which his reassurance and explanation rests. In addition to his own medical knowledge and the contributions of the internist, he must have imagination and be alert to the interrelation of the two branches. He needs, from his own special training, a thorough experience in the range and variety of human living. This particular training will give him the background of the social organization of the individual and the community in which he works. He will be most effective when his training leads him to accept man as a unit and as a social being, not as an entity composed of a mind and a body. The psychiatrist is far from infallible and should be eager to learn from his contact with the internist of all new developments in the field of internal medicine, physiology and pharmacology, since many of his own therapeutic tools have been contributed by those sciences.

The internist who hopes to make himself truly effective with his patients must be prepared to put aside any "mind-shy" attitude he may have. He has to learn to respect his patient as a person and train himself not only to see but to accept the rôle of the human facts. He must be constantly on the lookout for psychiatric problems as they arise, and be determined to give attention to the facts of his patient's life and living. He must be prepared to gain experience by trial and to add to his own awareness by his contacts with the psychiatrist. He must be determined to work with social facts and to modify them where he can. He must become sensitive to the problems of others. He should recognize that there are times when it is more constructive not to speak. He needs to cultivate a sense of responsibility for everything he says to a patient. As a member of a hospital staff he should learn to respect the social worker for what she can contribute in the way of understanding of his patients' background and in the modifications she can effect. He will have to gage what he can do alone and should be encouraged to ask for help when he is beyond his depth. He should obligate himself to learn what the atmosphere of his medical ward is. He needs to know how to carry out suicidal observation, to plan some activity for the convalescent days in bed. He should be willing to experiment with occupational therapy, hydrotherapy, such as continuous tubs, cold wet packs, and

physiotherapy. He should be sparing in the use of sedatives. He must be prepared to treat his own cases; not to transfer all such patients to a psychiatric ward.

To the internist who is genuinely desirous of a working relationship with the psychiatrist, a few words of advice may be helpful. Call the psychiatrist when help is needed. If there is any suspicion of factors outside the range of usual medical experience, ask for help. The psychiatrist welcomes conference and discussion and is anxious to give formulations in as simple and non-technical terms as possible. Do not be discouraged by psychiatric terminology. Insist that the psychiatrist use terms that you understand. When asking for consultation, state the reasons for doing so; only then can he best serve you. He needs to have all the medical findings and laboratory tests at his disposal; for this reason, conference with the internist before seeing the patient is highly desirable. Give the examiner a room with reasonable privacy in which to see his patient. Demand a conference with the psychiatrist after he has seen your patient. There are no mysteries he wants to withhold and, unless expressly requested not to do so by the patient, he likes to discuss all his findings with the physician. Since the patient is rarely able to accept all of the psychiatric formulation, do not show the patient the psychiatric report *in toto*. Try to use the psychiatrist's advice when it is given. If you trust him, you should be willing to accept his recommendations; if you intend rejecting his advice, there is no sense asking him in the first place. If the psychiatrist has to work as a member of a hospital, give him a status as a colleague and as a doctor. Do not make of him a specialist whose function will antagonize or frighten your patient. Give him an opportunity to teach, and take the opportunity yourselves to learn something about his science from your contacts with him. The psychiatrist has no desire to take over your cases unless specifically requested to do so and he wants to see the internist manage his own cases.

With such a program there is every reason to hope that the internist will once again resume his true function, namely, the treatment of the human being who is ill. He will then become the therapist of the person, no longer merely the therapist of a disease.

THE USE OF THE LOW TEMPERATURE BALL MILL FOR THE PREPARATION OF POLLEN EXTRACTS

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The method now most widely used in the preparation for clinical use of various pollen extracts is that suggested by Coca (1). In this procedure the dry pollen is first treated with ether to remove some of the lipoids and is then extracted for several days in the cold with an alkaline buffered solution. The latter aqueous extract is that used for diagnosis and treatment; the residue is discarded.

If this residue is examined under the microscope one finds that the appearance of the cells has not been materially altered by the several extractions (cf. Fig. 1, sections A and B). The cell walls remain intact and the cells are distinguished only with difficulty from the untreated material similarly suspended. The possibility at once suggests itself that, because it does not break the cell wall, the current method of extraction may fail to remove from the interior of the cell substances which might conceivably be of value in treatment or for the experimental study of pollen sensitivity; and conversely, that if the cells could be disrupted, extracts might be prepared without preliminary ether extraction which more closely approach the composition of the native pollen than do the extracts of the defatted, structurally intact cell.

There have been numerous attempts to produce such disruption of the cellular allergens preparatory to extraction. Freezing and thawing (2), grinding by hand in a mortar and pestle (3) with the aid of glass dust (4) or sand (5), protracted mechanical shaking with glass beads (6) or in a ball mill (7 and 8) have all been used, with varying degrees of success. In our experience the freezing and thawing technic, as well as grinding by hand, are relatively ineffective; while the protracted mechanical grinding in a ball mill may, in the light of

subsequent findings, be criticized on the ground that labile antigens deteriorate in the course of such treatment.

Mudd, Shaw, Czarnetzky and Flosdorf (9) have recently devised a low temperature ball mill for the disruption of bacteria and other cells, including pollen. As will be here shown, this mill modified in only one minor particular has proved remarkably effective in breaking up all the pollens so far tested (short ragweed, timothy, orchard grass and English plantain). When the ground powder is then extracted with simple salt solution for as little as one hour, a large proportion of the cell contents go into solution.

EXPERIMENTAL

The mill consists essentially of a hollow wheel in which 5 to 10 grams of the material to be ground is placed along with some stainless steel balls. It is essential that the material be thoroughly dried, and the small amount of moisture present in the native "dry" pollen must be first removed. This is accomplished by making a thick mush of the pollen with water, introducing this (and the steel balls) into the mill and attaching the mill to the Flosdorf-Mudd dehydrating ("lyophile") apparatus (10) for 24 hours. The inlet tube is then pinched off with a clamp and the mill is attached to a motor by which it is rotated in a bath of alcohol, acetone or some similar liquid kept at $-80°C.$ by the addition of dry CO_2. As the wheel rotates the steel balls within also rotate, and the dried material, rendered brittle at the low temperature, is ground and broken by their impact.

As originally recommended, the mill contains two heavy steel balls each $1\frac{1}{2}$ inches in diameter. It was found in the case of ragweed pollen that 6 hours of grinding broke only 50 per cent of the cells; but that if one also added 50 to 100 smaller balls of $\frac{3}{8}$-inch diameter, the larger surface they provided resulted in the breakage of well over 90 per cent of the pollen grains. After 4 to 6 hours grinding, water or salt solution is introduced through the inlet tube, the CO_2 bath is removed and the wheel is rotated at room temperature for 1 hour. The homogeneous creamy suspension is then removed with a pipette from the interior of the mill and the insoluble debris removed by centrifugation.

The microscopic appearance of this suspension is shown in figure 1, section C. The pollen of short ragweed (orchard grass, timothy and

plantain) is there shown before grinding, after extraction by the Coca technic and after extraction by the ball mill. Similar results have been obtained with orchard grass, timothy and plantain pollen. The small proportion of intact cells and the degree to which the broken cells are ground, are clearly shown in the figure. The supernatant fluid, which is essentially the water-soluble fraction of the entire cell, is distinctly opalescent in the case of all four of these allergens.

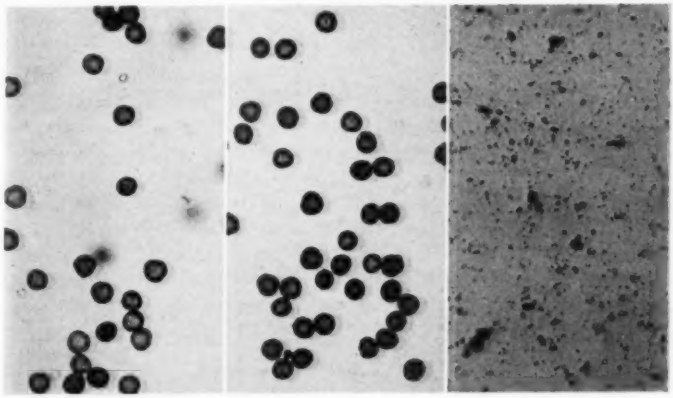

FIG. 1. RAGWEED POLLEN (MAGNIFICATION × 165)

A. Untreated.

B. Defatted with ether and extracted with alkaline buffer for 4 days.

C. Ground in ball mill and extracted with 0.85% NaCl for 1 hour.

Despite the fact that the ground pollen is not defatted and is extracted for only 1 hour with an unbuffered NaCl solution, the total solid and the total nitrogen extracted exceed those obtained by the extraction of the defatted intact cell for 4 days with alkaline buffer (Table I). Moreover, of the total nitrogen present in the extract, the protein fraction is usually higher in the case of the ball mill preparations, a significant finding in view of the fact that the protein content of the extracts is by some taken as the measure of their activity (11).

However, immunological and clinical studies on the ball mill preparation in comparison with the Coca extract of defatted but in-

tact ragweed pollen have failed to show any demonstrable differences. The antibody response in rabbits (12), the reagin-neutralizing capacity (13) and the clinical response of ragweed hayfever patients (14) were all essentially similar. Although further studies may disclose some additional factor or factors in the ball mill preparation not present in extracts of intact cells, such differences are not indicated by the investigations to date.

TABLE I

The Composition of Ball Mill Pollen Extracts Compared to Extracts of Defatted Whole Pollen[3]

Total Solids, Total Nitrogen, and Protein Nitrogen

POLLEN	TYPE OF EXTRACT	TOTAL SOLID CONTENT[2]	TOTAL NITROGEN[1]	PROTEIN NITROGEN[4]	PROPORTION OF PROTEIN NITROGEN TO TOTAL NITROGEN
		per cent	*per cent*	*per cent*	
Ragweed	Ball Mill	1.74	0.092	0.058	0.63
	Unbroken Pollen[3]	1.00	0.082	0.031	0.38
Timothy	Ball Mill	3.29	0.096	0.057	0.59
	Unbroken Pollen[3]	2.22	0.081	0.034	0.42
English Plantain	Ball Mill	3.23	0.081	0.029	0.36
	Unbroken Pollen[3]	2.26	0.07	0.012	0.17
Orchard Grass	Ball Mill	2.46	0.089	0.035	0.39
	Unbroken Pollen[3]	1.55	0.063	0.023	0.37

[1] In extract prepared by making 5 grams of dry pollen up to 100 cc. with extracting fluid.

[2] Electrolytes of extracting fluid already substracted.

[3] Defatted with ether and then extracted with alkaline buffer as described by Coca (1).

[4] Determined by phosphotungstic acid precipitation as described by Cooke and Stull (11): direct analysis of precipitate rather than supernatant fluid.

SUMMARY

Pollen is effectively broken and ground in the low temperature ball mill recently described by Mudd and his coworkers. The finely divided debris, on extraction for one hour with unbuffered NaCl solution, yields an opalescent extract which contains significantly more total solids, total nitrogen and protein nitrogen than that obtained by the usual methods of extraction. However, this difference

alone does not seem to justify the use of the ball mill for the preparation of pollen extracts for routine clinical use. As is discussed in the text, the immunological properties of this extract do not differ demonstrably from those of a buffered extract of defatted pollen (Coca extract).

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BOOK REVIEWS

The Morphology of the Brachial Plexus with a note on the pectoral muscle and its tendon twist. By WILFRED HARRIS. 117 pp. Illus. $8.00. (Oxford Medical Publications) *Oxford University Press, New York and London, 1939.*

The brachial plexus has always been of great interest to anatomists, and the present study is the most ambitious yet published on this subject. It was begun in 1902 and extended into 1938. During this time 158 plexuses were dissected, comprising specimens from 30 human beings, 6 anthropoid apes, 37 monkeys, and 85 other tetrapods and birds of all four classes. In 11 preliminary pages is offered a brief discussion of the morphology of the plexus and of established hypotheses. There is almost no mention of peripheral motor innervations and the possible correlation between individual muscles, their functions and groupings with regard to plexus arrangement, except that the last 15 pages are devoted to a discussion of "the pectoral muscle."

The information presented in this book is, perhaps, most noteworthy for two points developed. One is the fact that in some mammals, particularly those with long necks, the plexus is shortened or contracted to the extent that the fifth cervical nerve is not included; and even the sixth does not enter into its composition in the llama. The claim is made that this condition is characteristic of the most typically quadrupedal mammals, such as carnivores and artiodactyls, because of the lessened requirements in these of the deltoid muscle. But this type of plexus is found also in the mole, kinkajou, seal, and otter, and the author appears not to consider the fact that in carnivores and ungulates the deltoid takes on added importance for locomotion in its regular fusion with the spinal accessory muscle field.

The second point of chief interest is the author's logical hypothesis, based on sound argument, to account for the cutaneous innervation of a part of the dorsum of the hand by the ulnar and median nerves, and the innervation of some of the antibrachial muscles by an interosseous branch of the median in certain amphibians and reptiles. According to his belief, the fibers involved in these innervations are actually dorsal, from the eighth cervical and first thoracic roots, but instead of joining the posterior cord of the plexus these fibers, for some obscure reason, follow a ventral pathway.

Unfortunately the author has neglected to familiarize himself with the work of others in the same field. The monographic articles on the brachial plexus by Bolk, Kerr, and Miller are nowhere mentioned, and no reference is made to a single American paper or author, in spite of the fact that many such papers, and important ones, have appeared on this subject in standard American journals.

In consequence, the book contains many statements and conclusions, ostensibly original with the author, but already reported by others.

A. B. H.

Pediatric Nursing. By M. CORINNE BANCROFT, ELIZABETH PIERCE, AND BESSIE CUTLER. 3rd ed., revised and enlarged. 652 pp. Illus. *The MacMillan Company, New York, 1938.*

This book is divided into three parts, namely, Part I—Growth and Development of Children, Care and Nutrition; Part II—General Nursing Care; Part III—Nursing in Diseases of Infancy and Childhood. The list of references given at the end of each chapter is much more comprehensive than in the former edition, and the illustrations have been increased and improved.

Part I is an excellent treatment of the development of the normal child and his care. The principles laid down should be familiar to every nurse whether she is dealing with the child in the home or in an institution.

The second section, on general nursing care, is perhaps the weakest, and this weakness is manifest chiefly in the lack of consistency in the presentation of techniques and procedures. For example, very detailed equipment and procedure are discussed in some treatments such as intravenous injections of fluids, while treatments such as thoracentesis, lumbar puncture, etc., are discussed together under a general heading of "Fluids Obtained from Serous Cavities." For a book of this type, however, perhaps the more general discussion of specific treatments is preferable as there will necessarily be a variance in the equipment found in different hospitals.

The third section—"Nursing in Diseases of Infancy and Childhood"—is an excellent handbook for any nurse to have. A concise, readable description of practically all of the more common, and many of the less common, diseases of childhood, is given with the addition of a brief general discussion of the nursing care in connection with each disease.

A final improvement on the former text is an appendix which gives in outline form a very helpful list of play materials and books suitable for children in the different age groups from infancy to fifteen years.

This edition should be very useful to the student nurse because it serves not only as a ready reference but tends to stimulate further study by the extensive references given. It is in line with the modern trend in pediatric nursing in that the background of thought throughout the book seems to be the care and development of the normal, well child, and the preventive aspects of nursing care, which should be a paramount objective of all nursing.

M. E. R.